VOLUME 63 *April 1951* NUMBER 4

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS

The Teaching of Tuberculosis in Medical Schools. G. Canby Robinson 365
Correlation of Biologic Properties of Strains of *Mycobacterium* with Infra-red Spectrums. I. Reproducibility of Extracts of *M. Tuberculosis* as Determined by Infra-red Spectroscopy. Harrison M. Randall, Donald W. Smith, Ann C. Cole, and W. J. Nungester 372
The Role of the Bronchi in Pulmonary Tuberculosis. A Review Based on a Study of 305 Cases. Russell S. Jones and Frank H. Allen 381
Bronchogenic Carcinoma as a Differential Diagnostic Problem in Pulmonary Disease. III. Peripheral Type: Carcinoma Arising from the Minor Bronchi and Bronchioles. John H. Moyer and Alfred J. Ackerman 399
Benign Spontaneous Hemopneumothorax. Leroy Hyde and Bernard Hyde 417
Neomycin in Clinical Tuberculosis. David T. Carr, Karl H. Pfuetze, Henry A. Brown, Bruce E. Douglass, and Alfred G. Karlson 427
The Tuberculostatic Activity of Terramycin. Gladys L. Hobby, Tulia F. Lenert, Mary Donigian, and Daria Pikula 434
The Chemotherapy of Actinomycosis and Nocardiosis. Richard E. Strauss, Albert M. Kligman, and Donald M. Pillsbury 441
The Demonstration of Streptomycin-resistant Tubercle Bacilli in Necropsy Specimens. Edgar M. Medlar, Sidney Bernstein, and Frederic C. Reeves 449
An Evaluation of Media for Diagnostic Cultures of Tubercle Bacilli. Irene Melvin, George C. Klein, Warren Jones, and Martin M. Cummings 459
Clinical Comparison of Several Culture Media in the Diagnostic Demonstration of Tubercle Bacilli. C. Richard Smith 470
Case Reports:
Acute Disseminated Coccidioidal Granuloma. William Hentzel, J. K. Newton, and R. K. Hoskman 476
Löffler's Syndrome. Transient Pulmonary Infiltration with Eosinophilia. Charles A. Herken and E. Robert Wiese 480
Sensitivity of Tubercle Bacilli to Amithiosone (Myviasone). Mollie Mollov, Ida Hill, and Theodosius J. Kott 487
Correspondence:
Chemotherapy for all Active Tuberculosis. Emil Bogen and William H. Gatway, Jr. 490
Letter from Benjamin F. Miller 492
Books 493
American Trudeau Society: Reports of the Clinical and Laboratory Subcommittees 496
Abstracts 57

ANNUAL MEETING—CINCINNATI, OHIO
May 15–18, 1951
See inside back cover

Published Monthly at Mount Royal and Guilford Avenues, Baltimore 2, Maryland by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 19, N. Y.

Copyrighted 1951, by the National Tuberculosis Association

PRINTED IN U. S. A.

THE AMERICAN REVIEW
OF
TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY

EDITOR-IN-CHIEF
ESMOND R. LONG
Philadelphia, Pa.

MANAGING EDITOR
WALSH McDERMOTT
New York, N. Y.

EDITORIAL BOARD

W. EDWARD CHAMBERLAIN, Philadelphia, Pa.
HALBERT L. DUNN, Washington, D. C.
H. CORWIN HINSHAW, San Francisco, Calif.
KIRBY S. HOWLETT, Jr., Shelton, Conn.
JOHN C. JONES, Los Angeles, Calif.
ALEXANDER D. LANGMUIR, Atlanta, Ga.
JOHN D. STEELE, Milwaukee, Wis.
WILLIAM B. TUCKER, Minneapolis, Minn.
ARTHUR J. VORWALD, Trudeau, N. Y.

HELEN W. MILLER
Editorial Secretary

NOTICE TO SUBSCRIBERS AND CONTRIBUTORS

THE AMERICAN REVIEW OF TUBERCULOSIS is published by the National Tuberculosis Association and issued monthly about the first of the month. THE AMERICAN REVIEW OF TUBERCULOSIS is the official journal of the American Trudeau Society. A volume includes six numbers and begins with the January and July numbers.

Subscriptions: The subscription price of the REVIEW is $10 for the calendar year. Checks should be made payable to Collier Platt, Treasurer.

Character of the Review: The REVIEW invites the submission of original manuscripts on any phase of tuberculosis, nontuberculous pulmonary diseases, and related subjects of interest.

MANUSCRIPTS

Contributors are requested to pay particular attention to the following rules governing the preparation of manuscripts. Failure to follow these rules is a frequent cause of delay in the publication of articles.

Manuscripts should be sent in duplicate to the office of the Managing Editor, Dr. Walsh McDermott, 1790 Broadway, New York 19, N. Y., mailed flat, and transmitted by first-class mail with postage for return if not acceptable. They should be in English, double-spaced, typewritten on one side of the page, with wide margins. Tabular data should not be included in the text but should be presented in separate tables with appropriate reference in the text. All case reports should be written in complete sentences. Authors should exercise particular care in the preparation, notation, and description of figures and tables. References should be in REVIEW style. Each table must be accompanied by a descriptive title, and a suitable legend must be provided for each figure. Drawings must be made with india ink and all lettering should be made with a stencil. The quality of the reproduction of a roentgenogram depends upon both the quality of the original picture and of the glossy print obtained from photographing that picture. If a contributor does not have facilities available, preparation of figures or reproduction of roentgenograms may be handled through the REVIEW office. Under those circumstances, the contributor should supply a neat, properly proportioned, and suitably entitled drawing or the original roentgenogram, and will be expected to defray the cost of these services.

The publishers will not be responsible for manuscripts, illustrations, etc., lost in transit. In order to save expense for authors' corrections in proof, manuscript should be carefully revised by the author before submission.

Abstracts: Authors wishing to have abstracts of their papers appear in ABSTRACTS OF TUBERCULOSIS will facilitate their publication by sending concise abstracts or reprints to the Managing Editor.

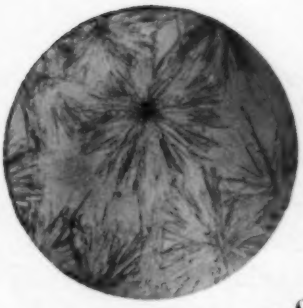
Reprints: Fifty reprints without covers of articles will be furnished to authors free of charge when requested in advance. A table showing cost of additional reprints with an order blank is submitted with proofs to the authors.

Single Copies: The price of single copies of this number of THE AMERICAN REVIEW OF TUBERCULOSIS is one dollar postpaid.

Advertising: Rates will be furnished by THE AMERICAN REVIEW OF TUBERCULOSIS, 1790 Broadway New York 19, N. Y. on request.

The Publishers reserve the right to decline any advertising submitted and to censor all copy. Acceptance of an advertisement does not constitute official endorsement of the product advertised.

Entered as second class matter March 3, 1917, at the post office at Baltimore, Md., under the Act of August 24, 1912. Acceptance for mailing at special rate of postage provided for in section 1103, Act of October 3, 1917. Authorized on July 3, 1918.



1941

A DECADE OF PROGRESS IN ANTIBIOTICS

1951

AMONG ALL the medical advances of the past ten years, progress in the development of antibiotics stands out as a major achievement.

On January 27, 1941, one hundred milligrams of penicillin, then a rarity, was first used in clinical medicine. At that time, Chas. Pfizer & Co. was called upon to apply its extensive experience in chemical manufacture and fermentation processes to the problem of large-scale penicillin production. In the intervening years, penicillin and other great antibiotics have come into world-wide use. And as the first antibiotic decade came to a close, Pfizer introduced Terramycin, the newest of the broad-spectrum antibiotics—an outstanding achievement of the past year.

Terramycin, product of a vast research program, represents a new phase of Pfizer's participation in the antibiotic field. Moreover, the development of Terramycin from experimental to clinical use within a matter of months, rather than years, demonstrates what can be achieved by the close cooperation of bacteriologists and other laboratory scientists, clinical investigators, and specialists in antibiotic production.

The decade ahead promises even greater achievements in the research and development of antibiotics for control of an ever-widening range of infectious disease.

Pfizer

ANTIBIOTIC DIVISION

CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*

MEAT...and the PROTEIN NEEDS of the DIABETIC

Not less but *more protein* than the traditional gram per kilo of body weight recommended for the non-diabetic individual promotes an increased sense of well-being in the diabetic patient. Liberal amounts of biologically excellent protein, such as that provided by *meat,* are therefore especially useful in dietotherapy.

For supporting the well-being and vigor of the patient, increasing his resistance to infection, and minimizing many of the degenerative changes common in diabetes mellitus, maintenance of body protein reserves is particularly important.[1,2] The former belief that protein foods, especially meat, engender hypertension and arteriosclerosis, is no longer tenable. On the contrary, deficits in dietary protein are apt to initiate anemia, hypoproteinemia, and retrogressive processes in the kidneys and other organs or tissues.

Ample amounts of high-quality protein foods in the prescribed diet—including generous amounts of meat—are important for maintaining a good nutritional state in the diabetic patient. Such a diet provides the nutritional essentials required in overcoming infections and in prompter healing of traumatic wounds.

Meat, however, is valuable to the patient for more than just its biologically excellent protein. It also furnishes important amounts of iron, thiamine, riboflavin and niacin, and of the newly discovered vitamin B_{12} which, among its several functions, promotes efficient utilization of protein.

---

(1) Mosenthal, H. O.: Management of Diabetes Mellitus: An Analysis of Present-Day Methods of Treatment, Ann. Int. Med., 29:79 (July) 1948.

(2) McLester, J. S.: Nutrition and Diet in Health and Disease, 5th ed., Phil., W. B. Saunders Company, 1949, page 364.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago...Members Throughout the United States

1 Simply snip off one end of PACKETTE with scissors.

PAS THERAPY

New Convenience in

2 Pour contents in 4 oz. of water — immediate and complete solubility.

Hellwig's PACKETTES are easy to prescribe and pleasant to take

The natural purity of Hellwig's Sodium Para amino Salicylate Dihydrate is preserved in individual, moisture-proof, polyethylene envelopes.

With Hellwig's PACKETTES the preparation of a single dose of P.A.S. no longer entails measuring powder or counting tablets. No chance of inaccuracy. Each envelope is pre-weighed. Each PACKETTE contains 4.18 grams of *neutral* Sodium Para amino Salicylate Dihydrate (4.18 grams being equal to exactly 3.0 grams of *free* Para amino Salicylic Acid). The difference in weight is due to the molecular weight of the sodium and moisture (dihydrate content).

50 PACKETTES IN A BOX

Hellwig, Inc. *209 E. Chestnut St. Chicago, Illinois*

Announcing: **SOLUTION** *of Crystalline*

Dihydrostreptomycin

Sulfate Merck

READY FOR IMMEDIATE INJECTION

This potent antituberculosis agent—preferred because it minimizes neurotoxic effects, and pain and swelling at the site of injection—now is supplied in "ready-to-use" form. SOLUTION OF CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK brings these significant advantages:

- ***No Refrigeration Required***
- ***Time-saving Economy***
- ***All-round Convenience***
- ***Clear, Colorless Solution***
- ***High Crystalline Purity***

AVAILABLE IN:

1 Gram (2 cc.) vials—500 mg. per cc.
5 Gram (10 cc.) vials—500 mg. per cc.

PARA-AMINOSALICYLIC ACID (PAS), when used in combination with Solution of Crystalline Dihydrostreptomycin Sulfate Merck, prolongs the effective period of chemotherapy by inhibiting or delaying the development of bacterial resistance; has proved effective also as the sole chemotherapeutic agent in selected cases of tuberculosis.

MERCK ANTITUBERCULOSIS AGENTS

SOLUTION OF CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK	PARA-AMINOSALICYLIC ACID MERCK (PAS)	CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

ROUTINE CHEST X-RAYS–

easy to take

easy to file

with FAIRCHILD'S

70mm FLUORO-RECORD CUT FILM CAMERA

Many hospitals are making routine chest x-rays as standard procedure on all admissions and "out" patients, and for periodic checkups on all hospital personnel. Not only does this routine procedure aid in the discovery of tuberculosis, but it also indicates signs of other chest ailments.

With its 70mm Fluoro-Record Cut Film Camera, Fairchild offers an inexpensive means of obtaining 2½ x 2½- or 2½ x 3-inch x-ray negatives. Each 6½ x 2 11/16-inch cut film sheet gives two individual x-rays or a stereo pair. This small exposure size simplifies filing in a minimum space – and yet, is large enough for easy interpretation.

The two-exposure cut film holder is accurately positioned for each exposure by either direct manual or remote electrical control.

The camera may be adapted for use with many types of existing x-ray equipment or procured with new photo x-ray units of leading manufacturers. See your supplier or write for more data to 88-06 Van Wyck Boulevard, Jamaica 1, N. Y., Dept. 160-11B 2.

Fairchild also makes the New Roll Film Cassette for angiographic studies . . . 70mm roll film cameras for mass chest x-rays . . . 70mm cut film and roll film viewers . . . 70mm film processing equipment . . . and the Chamberlain X-Ray Film Identifier.

Fairchild

CAMERA AND INSTRUMENT CORPORATION

the WILRO multi-purpose Bedside Lamp

Light where and when needed!

SCIENTIFICALLY CORRECT LIGHT—neither dazzling nor dim—patients, nurses, physicians see clearly, without effort, without eye strain.

INDIRECT ILLUMINATION—Wilro Reflector swings upright easily—provides restful, relaxing light for patients . . . extends usefulness of lamps.

BEDSIDE ACCESSIBILITY and Ease of Operation increase patients' independence and ability to help themselves—save nurses' time.

FULLY ADJUSTABLE *vertically*, as well as for *light angle* . . . direct light wherever wanted.

CONVENIENCE OUTLET in Night Light Dome (on Model K-66632 Lamp) for plugging in electric razor, radio, or other electric appliances . . . at finger-tip control.

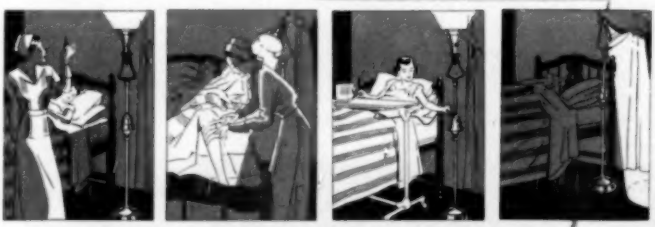
SAFETY is assured through foolproof, rugged construction. Designed and built to take abuse as well as meet all demands of normal use. Listed by Underwriter's Laboratories, Inc.

MODERATELY PRICED to fit hospital budgets.

Ask your Will Ross, Inc., representative about WILRO Multi-Purpose Lamps. Supplied with or without Night Light Dome.

SAFE

Listed by Underwriter's Laboratories, Inc. Every Wilro lamp carries this label.



Night Light Dome with switches and convenience outlet at bedside height.

WILL ROSS, INC.

MILWAUKEE 12, WISCONSIN

Manufacturers and Distributors of Hospital and Sanatorium Supplies and Equipment

THE AMERICAN REVIEW
OF
TUBERCULOSIS

VOLUME 63 *April 1951* NUMBER 4

THE TEACHING OF TUBERCULOSIS IN MEDICAL SCHOOLS[1]

G. CANBY ROBINSON

(Received for publication September 21, 1950)

The American program for the control of tuberculosis is now well established, and there is general agreement that the disease can be greatly diminished and eventually eradicated from this country if a large proportion of the people with the disease in an active, infectious form can be discovered, accurately diagnosed, isolated, and treated so that they cease to be a source of infection and can return to society with a minimum risk of a reactivation of the disease.

A major problem involved in the successful administration of this program is the provision of trained professional personnel in sufficient numbers to carry out effectively the various component parts of the program. A larger number of doctors, nurses, social workers, and other trained persons are needed than are now available, and a wider interest in the broad aspects of tuberculosis control among the medical profession generally is highly desirable.

The effectiveness of the campaign is dependent primarily upon the interest, understanding, and skill of the medical and nursing professions in this field, increased attention to the social and economic problems of tuberculosis, and well-organized programs in all public health departments for combating the disease.

Adequate physical facilities and sufficient public funds for their operation can now usually be obtained in our states to meet the requirements of the tuberculosis program wherever effective leadership is developed. The supply of efficient personnel for effectively utilising the present-day knowledge of tuberculosis is, however, inadequate. At present, there is a definite shortage in this country of professional personnel for the institutional care of tuberculosis patients, which improvements of institutions, remuneration, and professional opportunities have failed to overcome. Greater effort is needed to stimulate the interest of doctors, nurses, social and rehabilitation workers, so that more of them will be attracted into the field of tuberculosis. A fundamental basis for this effort is to give the students of medicine, nursing, and social work a better chance to learn about and understand the significance of this work as a field of valuable service and of satisfying professional opportunities, especially at the time when they are deciding on the lines of work in which they wish to engage.

[1] Address presented before the Southern Tuberculosis Conference at Roanoke, Virginia, September 21, 1950.

It is, therefore, important for all those interested in this campaign to realize the need for stimulating and supporting plans for improvement of the teaching of tuberculosis in our schools of medicine, public health, nursing, and social work, in order to have an increasing number of their graduates not only understand the various problems of the disease, but also desire to take part in their solution.

While the subject of this paper is the teaching of tuberculosis in medical schools, it is a fair assumption that, if this teaching is given greater emphasis and broader scope than now exists in most of our medical schools, its influence will be strongly felt in nursing and medical social-work education. The study of tuberculosis should be given a prominent place in medical teaching because of its value in the education of every doctor, regardless of the field of medicine he ultimately enters. There is no disease from which a medical student can learn so many principles of medical practice as from the study of pulmonary tuberculosis.

First of all, the diagnosis of this disease is one of the best experiences the student can have in utilizing and correlating the various technical diagnostic procedures he is taught. It is necessary to bring together the medical history of the patient, the results of his physical examination, various laboratory and roentgenographic studies, and various special procedures which generally serve to give a definite diagnosis and evaluation of the patient's disease when pulmonary tuberculosis is present. There are few diseases in which an accurate and inclusive diagnosis is more important, as it is fraught with such harassing consequences for the patient and his family.

The positive diagnosis of pulmonary tuberculosis leads to the serious problem of the management of the patient and creates a situation in which the doctor-patient relationship is of paramount importance. This situation involves consideration of the social and economic status, the emotional reactions, and the personality of the patient, information that is best obtained by the medical social worker. First, the diagnosis of the disease is made, and then the diagnosis or evaluation of the patient as a person is required in order to formulate a plan of treatment that should give each individual patient the best chance of recovery. This is a very valuable lesson for the medical student, and he should be given the opportunity to participate directly in the whole process.

As tuberculosis is a communicable disease, it is required by law to be reported to the health department. The comprehensive study of a tuberculosis patient should serve to lead the interest of the student into an important phase of public health and preventive medicine, by which he would be introduced to the epidemiology of tuberculosis, the functions of the health department, the role of the public health nurse, the examination of contacts, and case finding by mass roentgenographic surveys. A better understanding and interest in the public health aspects of tuberculosis by all doctors would be of great value in its control, and seeds sown in this field in their student days will surely bring forth some valuable crops later on.

The study of the treatment carried on in a tuberculosis hospital gives the student an opportunity to learn about the medical care of chronic illness, procedures and precautions required because of the communicable nature of the

disease, how bed rest is maintained, and how it is supplemented by surgical procedures and specific drug therapy. The student would also be given an understanding of the broader aspects of medical care, including the contributions of the medical social worker, the occupational therapist, and the librarian, and of the way in which plans are made for vocational rehabilitation, all of which should be part of the education of every physician.

An understanding of the importance of educating the patient so that he may learn to live safely on the basis of his own knowledge of his disease is of much value to the student as a concept of wide application in medical practice. This can be learned nowhere better than in a tuberculosis hospital.

There are three essentials for effective teaching of clinical medicine: enthusiastic, well-educated teachers, broadly experienced in the field they undertake to teach; available clinical material in the form of patients presenting various phases of the disease to be studied; adequate facilities for the thorough study of these patients.

In regard to the first essential, the qualified teacher, the Committee on Undergraduate Medical Education of the American Trudeau Society (1) has stated:

> The student's interest can be stimulated most effectively through the efforts of his own teachers; in all instances where the subject is adequately presented by experienced and enthusiastic instructors, it is equally enthusiastically accepted by the students as a necessary part of their training. Therefore, it is thought best to turn the Society's attention to the stimulation of interest among deans and faculties in providing training through the medium of highly qualified teachers.

The second recommendation of the Committee is that the study of tuberculosis cannot be separated fruitfully from that of other pulmonary diseases, and it advocates the encouragement of the attitude that pulmonary tuberculosis be not considered as a disease apart from other pulmonary diseases in the organization of teaching. The teaching of tuberculosis should take its place as an integral part of the teaching of clinical medicine.

In order to have these recommendations become effective in our medical schools, it is not only necessary to stimulate interest among their deans and faculty, but it is essential to gain the interest and the wholehearted support of the professor of medicine. It is primarily through his efforts that adequate time will be allotted in the curriculum and the required teaching staff will be provided for skillful instruction and training in tuberculosis. It is very important to have an influential member of the department of medicine to direct and correlate the teaching of tuberculosis in all of its phases and to stimulate and conduct medical research in this field.

The first phase of the teaching is diagnosis of the disease and study of the patient who is its victim, so that a plan of management may be initiated in each individual case. This phase should be conducted in an outpatient clinic for pulmonary diseases, where all patients having symptoms or physical evidence of respiratory disorders, who are admitted to the teaching services of the hospital, should be referred. Here, as well as in the teaching wards of the hospital, a broad view of pulmonary diseases should be maintained, with pulmonary

tuberculosis considered as a highly important form of the various diseases to be differentiated and studied. As a part of the facilities of the clinic, adequate laboratories and expert roentgenologic services, readily available for teaching purposes, are essential and may be expected to be available as facilities of all of our medical schools.

When the positive diagnosis of pulmonary tuberculosis is made, the patient should have special attention of a staff member with time, interest, and experience for determining what his future course should be, in order to give him the best chance of recovery. Here is where the qualified specialist in tuberculosis and adequate medical social service have an important part to play. As has already been indicated, here the medical student can learn valuable lessons in the management of patients if he is allowed to participate fully in the process of evaluating the patient as an individual, which must take into consideration his emotional reactions, his personality characteristics, and what can be expected of him as a person.

The second phase of teaching is concerned with treatment of the disease and isolation of the patient. The tuberculosis hospital, as has been pointed out, presents valuable opportunities for all students of medicine. The Committee on Undergraduate Medical Education states in its report (1) that tuberculosis hospitals are of great value as educational institutions, and that "the clinical experience of their staff members should be utilized fully for the benefit of the students." In recommending that emphasis be placed on the integration of education in pulmonary diseases with all other phases of internal medicine and surgery, the Committee, however, emphasizes the desirability of a connection between the medical teaching center and the tuberculosis hospital.

The provision of hospital teaching services may present difficulties for many medical schools, as there may be no tuberculosis hospital conveniently near the medical school that is adequately organized to carry on medical education. Definite progress is being made in overcoming these difficulties. Teaching services in tuberculosis are now integral parts of some teaching hospitals, such as in the hospitals of the Jefferson Medical College and of Howard University, and in the New York Hospital, the teaching hospital of the Cornell University Medical College.

Excellent hospital teaching facilities have been provided by a number of medical schools, as reported by Charles A. Doan (2). The reason for this progress has been the general acceptance of the idea that tuberculosis hospitals should no longer be located far from urban centers and preferably in mountainous country, but that they should be in close proximity to, or an integral part of, a medical center where all forms of medical service are available for all patients.

This aspect of teaching has recently been well discussed by Doctor Doan, Dean of the Ohio State University College of Medicine and also a Director of the National Tuberculosis Association, before the Association of American Medical Colleges. His paper on Education in Diseases of the Chest was prepared and presented at the request of the Committee on Medical Education of the American Trudeau Society. A description was given of the forward-looking plan for teaching tuberculosis at the Ohio State Medical College, where Doctor Doan is also

professor of medicine, forming a fortunate setup for the teaching of tuberculosis in that institution.

The most important forward step that has been taken relative to the provision of facilities for hospital teaching has been the policy of the Department of Medicine and Surgery of the Veterans Administration. Among the objectives of the Veterans Administration hospitals, as stated by Dr. Paul B. Magnuson (3), Chief Medical Director, are the following: To secure the services of outstanding medical men to serve as teachers, consultants, and attending physicians, and to build new hospitals in urban centers in close proximity to medical schools and medical talent, and to attempt to make every VA hospital a teaching hospital. Veterans' hospitals, so located, are operated by what is known as the Deans Committee which gives an official and close integration with the medical schools.

The relationship of Veterans' tuberculosis hospitals and medical schools has been fostered by Dr. John B. Barnwell, Chief of the Tuberculosis Division of the Veterans Administration, and he stated, as quoted by Doctor Doan, that "as a part of the Veterans Administration, there are 22 hospitals with tuberculosis services which might be used for the teaching of undergraduate students." The opportunity for medical students to serve as clinical clerks in these hospitals under very favorable conditions has been legally provided for.

When adequate provisions can be made for a hospital teaching service, students should be assigned to the hospital, in groups of convenient size, to spend the equivalent of two or three full weeks at the hospital. If the distance is far from the medical school, arrangements for full-day attendance with provision, if possible, to have students reside in the institution should be made.

Students, especially those with particular interest in tuberculosis, should be encouraged to spend time during their summer vacations in tuberculosis hospitals, as they have been doing in small numbers for some years at the Ray Brook New York State Hospital and at the Trudeau Sanatorium, with much satisfaction to the institutions.

The third phase of teaching tuberculosis in medical schools is the study of the public health aspects of the disease. In the program of teaching public health and preventive medicine now conducted in all of our medical schools, tuberculosis should be given a prominent place, and the study of its public health problems should be correlated, as far as possible, with the study of individual cases of the disease. The teaching should be conducted with the cooperation of the local health department serving, in a sense, as the laboratory of public health. In this way the student may learn the purposes for the reporting of tuberculosis to the health department, how the register is operated, how case finding is conducted, and the significance of the number of cases reported annually relative to the annual tuberculosis death rate and to the whole program of the control of the disease. Attention should be given also to the social and economic problems that are created by tuberculosis and to its relation to industrial medicine. The functions and operation of the voluntary tuberculosis association should also be discussed. There is no disease offering as wide a view of public health problems as tuberculosis.

The fourth phase of the teaching is a systematic course of lectures and clinics

to an entire class, as part of the course of internal medicine, planned to augment and correlate the clinical work of the students. These lectures should cover, broadly, the clinical aspects of pulmonary tuberculosis, including not only the diagnosis and the principles of medical and surgical treatment, but also the physician's part in the control of the disease; the emotional, social, and economic problems it creates and what may be done about them; and the general principles of rehabilitation and aftercare of patients. It would require a number of specialists in various forms of tuberculosis and twelve or more teaching hours to give such a correlated course of lectures.

A program of teaching tuberculosis is here presented consisting of the study of broadly considered diagnostic problems of tuberculosis as part of the study of pulmonary diseases, a clinical clerkship in a tuberculosis hospital, instruction in the public health aspects of the disease, and a systematic course of lectures and clinics. This plan is presented with the conviction that, if earnestly and effectively carried out, such a program would improve the present teaching of tuberculosis in our medical schools. To answer the question as to whether this field of teaching needs improving, it may be said that the American Trudeau Society Committee believes that its investigations thus far have demonstrated that "instruction in this field requires more improvement than is the case in other fields of comparative importance." This is a conservative statement.

This program is presented also with the conviction that it would be a valuable part of the education of all medical students, regardless of their future fields of work; that it would serve to stimulate greater interest in tuberculosis, leading a larger number of physicians to devote themselves to this phase of medicine; and that it would engender wider understanding of the problems of tuberculosis and greater cooperation in control of the disease by the medical profession in general. If these results can be obtained, they would affect very favorably the efficiency of the program for control of tuberculosis in this country.

Finally, the question must be raised as to whether improvement of the teaching of tuberculosis in medical schools should be the concern of tuberculosis associations. The problem must be recognized as being highly technical and requiring the leadership of specially qualified members of the medical profession. With such leadership, however, there would seem to be no reason why a state association should not undertake to create a relationship with the medical schools in its state through which it could show its interest in, and gain an understanding of, their teaching of tuberculosis.

A state committee could learn the strength and weakness of their medical schools in this field, what their needs are, and how the state association, guided by the American Trudeau Society and the National Association, might formulate a program of assistance in teaching.

Without attempting to say what this program should be, as it probably would differ in every state, consideration must be given to the question of whether it would be wise to utilize some of the millions of dollars contributed annually through the Christmas Seal Sale for the improvement of the teaching of tuberculosis in medical schools. It is evident that this question is already in many minds,

and it seems to be gaining national approval. The Subcommittee on Medical Schools and Hospitals of the Medical Education Committee of the American Trudeau Society recently voted that:

> The principles of having Seal Sale funds utilized to advance the teaching of pulmonary disease to medical students be recommended to the Joint Committee on Program Development as a part of Authorized Activities of Tuberculosis Associations.

A questionnaire has already been circulated by the National Tuberculosis Association to ascertain whether funds are being expended for medical education, and the Committee has taken steps to determine what may be done to promote the principle. At least one state, Wisconsin, already has given financial assistance to one of the medical schools in its state for the teaching of pulmonary disease.

Tuberculosis associations cannot be expected to contribute sufficient funds for the basic support of the teaching of tuberculosis, but they cannot expect medical schools to devote increased funds for the needs in this field at this time, as their financial situation is indeed serious. The medical schools of this country incurred in 1948 a combined deficit of approximately $10,000,000 (4), and some of them are in a precarious state of existence. This is an added argument in favor of the proposition that, if tuberculosis associations are convinced that improvement of medical teaching in tuberculosis in the medical schools of their states is needed to forward control of the disease, they should be concerned with the problem of finding funds to finance this improvement. A state program for this purpose has a state-wide appeal and should attract extra support from all local associations beyond the Seal Sale percentages they pay.

It is, however, by no means only financial support of teaching with which tuberculosis associations should be concerned. They should make every effort to publicize the needs and advantages of tuberculosis teaching in their medical schools after they are reliably informed what the improvements should be.

Public education has been the basic function of tuberculosis associations since the inception of the National Association. Should not now greater attention and concern be given to the education of the professions that are essential for the control of tuberculosis?

A somewhat detailed discussion of a plan for the improvement of the teaching of tuberculosis in medical schools has been presented, so that the problem may be given thought along definite lines and defined for discussion, with the hope of arousing interest in a fundamental factor in the control of tuberculosis, namely, the improvement of teaching of tuberculosis in our medical schools.

REFERENCES

(1) Report of the Committee on Undergraduate Medical Education, Am. Rev. Tuberc., 1946, *54*, 456.

(2) Doan, C. A.: Education in diseases of the chest, J. A. Am. M. Coll., 1950, *25*, 90.

(3) Kracke, R. R.: The medical care of the veteran, J.A.M.A., 1950, *143*, 1321.

(4) Medical Education in the United States, National Fund for Medical Education, Inc., March, 1950, p. 16.

CORRELATION OF BIOLOGIC PROPERTIES OF STRAINS OF MYCOBACTERIUM WITH INFRA-RED SPECTRUMS[1,2]

I. Reproducibility of Extracts of *M. Tuberculosis* as Determined by Infra-red Spectroscopy

HARRISON M. RANDALL, DONALD W. SMITH, ANN C. COLM, AND W. J. NUNGESTER

(Received for publication December 4, 1950)

INTRODUCTION

In recent years biologic research has employed an ever increasing number of effective tools of a purely physical character, namely, X-rays, electrophoresis, the ultracentrifuge, and radio isotopes to mention only four. The successful application of infra-red spectroscopy to many diverse problems in chemistry and the chemical industries and to certain uses in the biological field (1, 1a) suggests the value of a systematic study of its possibilities in the field of tuberculosis.

In working with biologic materials which may be unstable, discriminating physical examinations of initial, intermediate, and end products are most helpful. A great advantage of infra-red spectrophotometry is that it can be used with a minimum of damage to unstable substances and with considerable discrimination. Hence, in the study of biologic properties of extracts of *M. tuberculosis* not unlike those previously investigated by Borissjak, Sieber, and Metalnikow (2), Anderson (3), and Choucroun (4), the practicability of applying this technique as a control to the fractionation procedures has been examined.

PLAN OF INVESTIGATION

The present research employs fractions of several strains of *M. tuberculosis*. These fractions are complex mixtures obtained by extracting masses of tubercle bacilli with chloroform. In one case, further separations were made to obtain acetone-soluble and acetone-insoluble fractions and alcohol-soluble and alcohol-insoluble fractions. It is the purpose of this study to determine if the mixtures present in these extracts, prepared under standard conditions, would give rise to reproducible infra-red spectrums which would be characteristic for the microorganism from which the extract was made.

The two prime considerations of reproducibility and specificity must first be determined before the procedure can be accepted as useful. The reproducibility of spectrograms of culture extracts would probably depend on the strain of culture, its age, medium used, methods for extracting, conditions and time of storage of extracts, and the techniques used in making the spectrograms. The results to be

[1] From the Departments of Physics and Bacteriology, University of Michigan, Ann Arbor, Michigan.

[2] Aided by grants from the Veterans Administration and the Horace H. Rackham School of Graduate Studies of the University of Michigan.

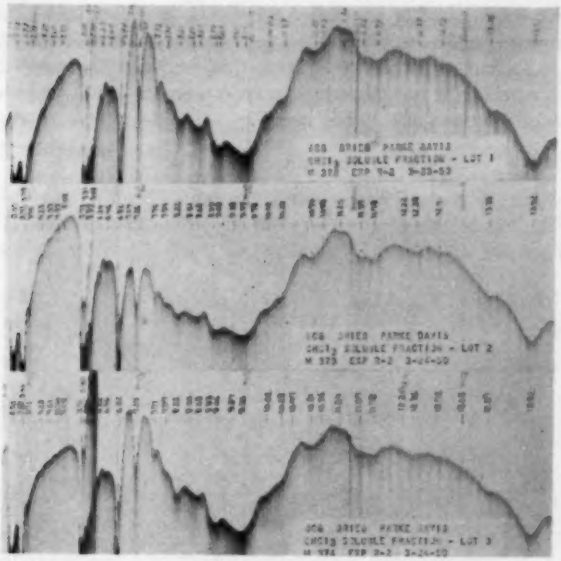


PLATE 1. Spectrums of chloroform-soluble fractions from dried BCG

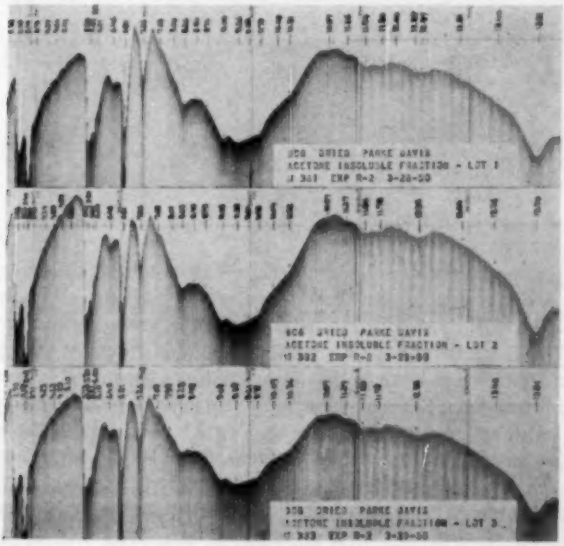


PLATE 2. Spectrums of acetone-insoluble fractions from dried BCG

reported were obtained after an earlier experience in which the biologic factors, age of culture in particular, were not adequately controlled. After corrections were made, a second series of experiments was carried out which was designed to determine whether or not reproducible spectrograms would be obtained from multiple lots of fractions of tubercle bacilli.

OBSERVATIONS

Spectrums from extracts of a given lot: Three sets of fractions were prepared by the same technique from a given stock of dried BCG organisms, using chloroform followed by acetone and alcohol precipitation. The 3 chloroform-soluble fractions

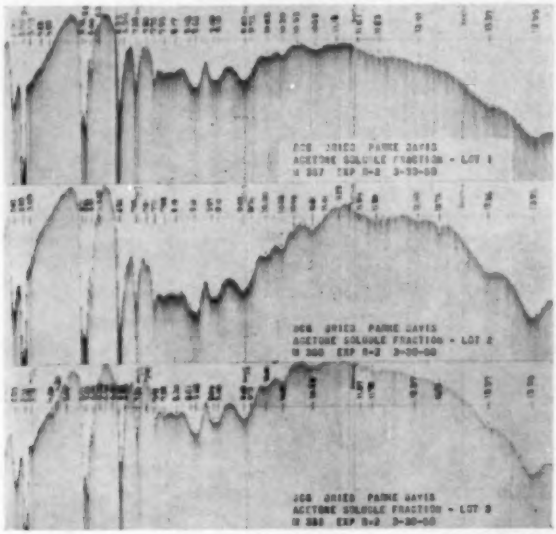


PLATE 3. Spectrums of acetone-soluble fractions from dried BCG

do in fact give spectrums that are identical, as shown by the three reproductions of Plate 1. A single sample, run three times, would not have given more similar spectrums. The close similarity existed for both the wave-length values and the contours. The 3 spectrums of the acetone-insoluble fractions, the group of 3 recorded on Plate 2, are alike in wave-length values as well as in contours. The third set of 3 fractions, the acetone-soluble fractions, give the spectrums reproduced in the three reproductions recorded on Plate 3. Again, these are quite definitely the same. The spectrums of the 3 alcohol-soluble fractions and 3 alcohol-insoluble fractions are not reproduced, but for each fraction the 3 spectrums are the same. Within any group of 3 spectrums, the wave lengths are the same within the set degree of accuracy of measurement, namely $\pm .03$ mu. There are many absorptions common to all of the spectrums, but there are for each

fraction bands which characterize that particular fraction, and these bands together with the contours are sufficient to distinguish the fractions. Accordingly, it appears that, when the organism used comes from a homogeneous source, the results are reproducible for the several fractions and that the spectrums of the several fractions are sufficiently different in their wave lengths and contours to distinguish between these fractions.

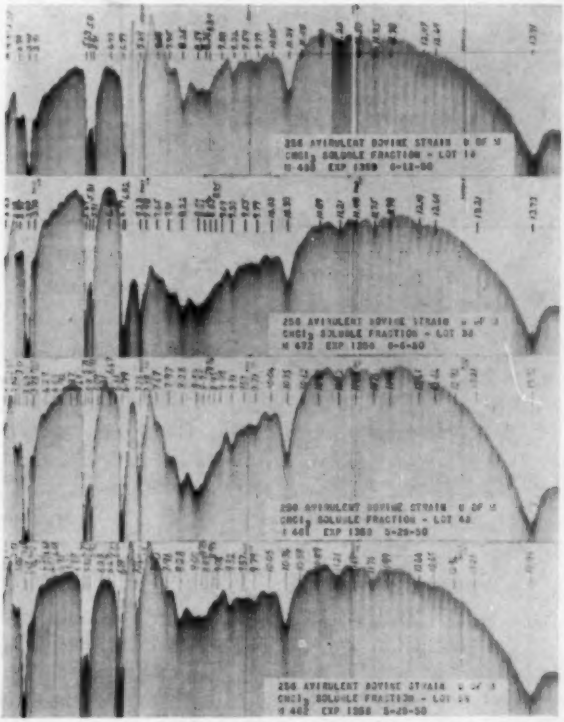


PLATE 4. Spectrums of chloroform-soluble fractions from an avirulent bovine strain

Spectrums of extracts from various lots of living organisms: To test spectroscopically the reproducibility of culture growths and their fractions, 8 flasks of malic acid medium (modified Long's) were inoculated from a single culture of a 14-day-old laboratory strain of an acid-fast organism, designated as BCG. As this culture was carried for some years without special procedures, it will hereafter be referred to as strain 256. When the culture growth had reached the edges of the flask, a new set of 8 flasks of malic acid medium was inoculated. At this point, an inoculum was taken in turn from each of the first 8 flasks to inoculate a corresponding flask of the second set. The same procedures of inoculation,

growth, harvesting, and fractionation were followed as closely as possible in the case of each of the flasks in the group. Thus it was possible to prepare fractions from 8 cultures which had arisen from a common inoculum. The spectrums of the chloroform fractions of 4 of the 8 cultures are shown in Plate 4. They are characteristic of the entire 8 cultures. These spectrums agree in wave length values within the set accuracy. They also show these absorption bands in very nearly the same relative intensities in all the spectrums. There is a very high degree of reproducibility for the chloroform fraction.

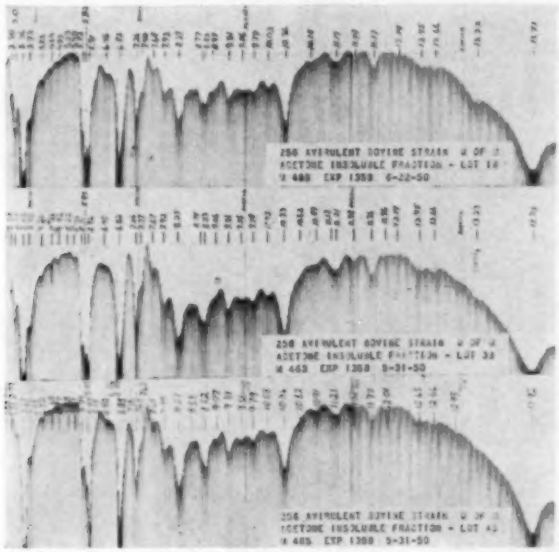


PLATE 5. Spectrums of acetone-insoluble fractions from an avirulent bovine strain

A second set of fractions, the acetone-insoluble fractions(Plate 5), gave spectrums alike to a similar degree to that found for the chloroform fractions. However, they differed sufficiently from the chloroform fractions so that the two fractions can be distinguished by their spectrums. The spectrums for the acetone-soluble fractions are not reproduced here. The foregoing has shown that when all processes are carefully controlled it is possible to obtain spectrums characteristic of a given fraction of an organism.

Spectrums of extracts from H37Rv strains obtained from various laboratories: As a further instance of reproducibility, the spectrums of Plates 6 and 7 are to be compared. In this instance, as the captions show, the cultures have been obtained from a number of different laboratories. The strain is common, H37Rv, but the medium on which the cultures were grown may have differed from laboratory to laboratory. Before examining the spectrums of extracts of the cultures, each cul-

ture was transferred three times on malic acid medium. All of the procedures were standardized. The spectrums of the several cultures may be compared, therefore, for possible differences in the cell composition arising from the past history of the cultures. There is in fact a marked likeness between the spectrums of the chloroform-soluble fractions of the H37Rv strains irrespective of their source. However, several intensity variations are noticeable. For example, the absorption

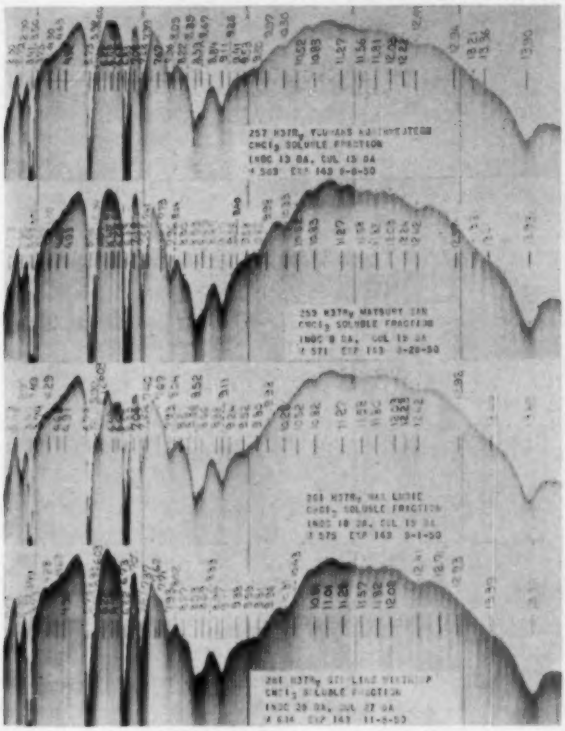


PLATE 6. Spectrums of chloroform-soluble fractions of H37Rv cultures received from various laboratories.

at 12.4 μ is generally weak, but is definitely stronger in 289A. Similarly the very weak absorption at 6.48 μ assumes strength only in 261A. Likewise, the sharp band at 5.93 μ found in a number of the spectrums becomes in the others only a change in slope on the strong absorption at 5.72 μ. The pair of absorptions at 8.53 μ and 9.11 μ have the band at 9.11 μ, the weaker of the two, but in 281A it approaches 8.53 μ in strength while in 286A it is definitely stronger. It was noticed that the culture medium of strain 286 was cloudy while all the others were clear. Hence

a change in the chemical composition of this particular culture would not be altogether unexpected.

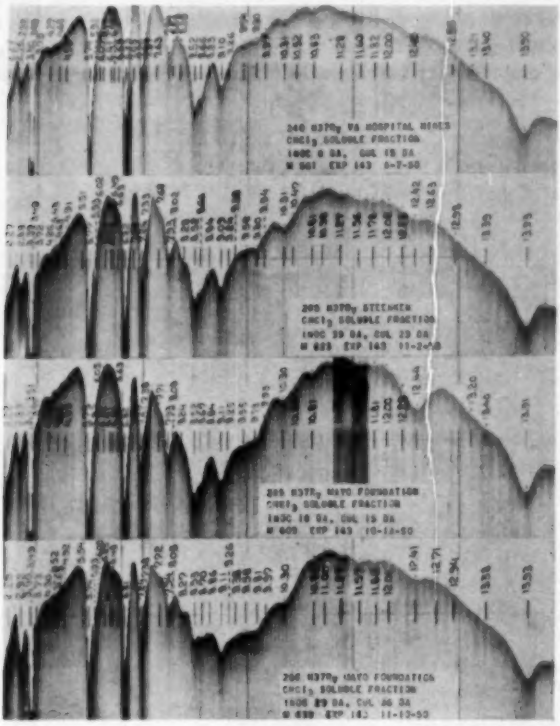


PLATE 7. Spectrums of chloroform-soluble fractions of H37Rv cultures received from other laboratories.

COMMENT

The present study is an exploratory research to determine to what extent the infra-red spectrums of the complex mixtures which compose the various fractions of the tubercle bacillus may be used in bacteriologic investigations of this organism. It has been established that, with sufficient care in preparation, the different fractions can be reproduced to the extent that they give constant spectrums, and that the spectrum of each fraction is characteristic of that fraction. The spectrum may therefore be used as a control over the processes of inoculation, growth, harvesting, and fractionation in the production of fractions to be tested for biologic activity.

It is suggested that this method may be applied as a control procedure in the

preparation of antigenic fractions; to differentiate between strains of tubercle bacilli; to point out possible chemical differences between drug-resistant and -sensitive strains; and to detect differences between virulent and avirulent cultures of tubercle bacilli.

SUMMARY

Successful reproducibility of spectrums of extracts of *M. tuberculosis* has been demonstrated. Such reproducibility depends upon strict adherence to a plan for, growth of cultures, their fractionation, and subsequent preparation of samples.

It has been established by the present work that each of several fractions of a particular microorganism has its own composite spectrum sufficiently characteristic to differentiate it from other fractions.

It has been established that this method may be employed as a control in the growth and fractionation of cultures.

SUMARIO

Correlación de las Propiedades Biológicas de Cepas de Mycobacterium con los Espectros Infrarrojos

Queda demostrada la reproducibilidad de los extractos de *M. tuberculosis*. Esa reproducibilidad depende de la absoluta conformidad a un plan fijo para la siembra de cultivos, fraccionación de los mismos y preparación subsiquiente de muestras.

Queda establecido por la labor actual que cada una de varias fracciones de un microbio dado posee su propio espectro compuesto, suficientemente típico para diferenciarlo de otras fracciones.

Queda establecido que cabe emplear esta técnica como control del desarrollo y la fraccionación de los cultivos.

RESUME

Corrélation des propriétés biologiques des souches de Mycobactérium et leur spectre infra-rouge

La possibilité de la reproduction d'extraits de *M. tuberculosis* a été démontrée. Cette possibilité de reproduction dépend d'une stricte adhésion à une méthode déterminée pour, le développement des cultures, leur fractionnement et, ensuite, pour la préparation des échantillons.

Le présent travail a établi que chacune des différentes fractions d'un organisme donné possède son propre spectre, qui est suffisamment caractéristique pour permettre de le différencier des autres fractions.

Il a été établi que cette méthode peut être utilisée comme méthode de contrôle pour le développement et le fractionnement des cultures.

REFERENCES

(1) KLOTZ, I. M.: Infra-red spectra of some proteins and related substances, J. Am. Chem. Soc., 1949, *71*, 1615.

(1a) Blout, E. R., and Mellors, R. C.: Infra-red spectra of tissues, Science, 1949, *110*, 137.
(2) Borissiak, Sieber, and Metalnikow: On the question of immunisation against tuberculosis, Ztschr. Immunitätsforsch. u. exper. Therap., 1911, *18*, 65.
(3) Anderson, R. J.: The separation of lipoid fractions from tubercle bacilli, J. Biol. Chem., 1927, *74*, 525.
(4) Choucroun, N.: Tubercle bacillus antigens: Biological properties of two substances isolated from paraffin oil extract of dead tubercle bacilli, Am. Rev. Tubere., 1947, *56*, 203.

THE ROLE OF THE BRONCHI IN PULMONARY TUBERCULOSIS[1]

A Review Based on a Study of 305 Cases

RUSSELL S. JONES AND FRANK H. ALLEY

(Received for publication October 9, 1950)

INTRODUCTION

The pathogenesis of tuberculosis, like that of many other diseases, is complex and dependent upon many factors diverse in character, interrelation, and classification. In the broadest grouping these factors may be related to the infecting bacilli (as number, strain, virulence) and to the reacting host (as age, resistance, hypersensitivity, immunity, and anatomic structure). Many of such terms are nebulous, however, and are comprised, in turn, of other variable aspects. For example, "virulence" depends upon the reaction between parasite and host, while "resistance" may be related to age, nutrition, physical habitus, and similar factors. The pathogenesis of pulmonary tuberculosis has not been clarified by the division of the study of the host reaction among the different biologic sciences (physiology, biochemistry, serology, pathology) or by use of the terminology of causal relationship (predisposing, inciting, aggravating, complicating). One must agree with Pinner (1) that "a critical analysis reveals that a recognition of phthisiogenetic factors rests almost exclusively on implication, analogy, deduction, and not on direct observation of clinical and pathological processes."

Nevertheless, some approach to evaluating the diverse factors and delineating the pathogenesis of tuberculosis should be made. Many aspects must await the advance in general knowledge of host reactions. With our present knowledge, the factors most readily subject to careful study are the morphologic ones, such as those concerned with specific anatomic features of the involved organ.

It is the purpose of this paper to present the various forms of tuberculous bronchitis in man and a concept of the role of the bronchi in the pathogenesis of pulmonary tuberculosis.

METHODS AND MATERIALS

This report is based upon the study of the lesions of pulmonary tuberculosis in man, encountered in 105 autopsies and 200 resected lungs, lobes, and/or bronchopulmonary segments, and studied by one or both of the writers. In 18 autopsies and 155 surgically resected specimens at the West Tennessee Tuberculosis Hospital, a thorough pathologic examination was made by the following method:

The pulmonary tissue was re-expanded to its approximate intrathoracic dimensions by introducing into the bronchi 10 per cent formalin under low-gravity pressure. After proper

[1] From the Division of Pathology and Bacteriology, University of Tennessee College of Medicine, West Tennessee Tuberculosis Hospital, John Gaston Hospital, and Oakville Sanatorium, Memphis, Tennessee.

fixation, usually four to seven days, the lungs were serially sectioned. The parallel planes of sectioning were along the apicobasilar axis and perpendicular to the mediastinum. The sections thus made were comparable to postero-anterior roentgenograms. The dissecting microscope was utilized for the study of the finer macroscopic details of the pulmonary changes. In some instances thin sections of lung were cleared in methyl salicylate or in alcohols and xylol similar to the procedure for the paraffin embedding of tissue.

Blocks of tissue from labeled areas of the pulmonary tissue were then examined microscopically. Three microsections, usually serial, were made and stained with (*1*) hematoxylin and eosin, (*2*) carbol-fuchsin and hematoxylin, and (*3*) a combined connective tissue stain for simultaneous demonstration of elastin, reticulin, and collagen. In caseous tissue the preserved reticulum and elastic fibers often outline the pattern of the formerly intact pulmonary tissue. Not only can one frequently identify the alveoli, bronchi, and blood vessels in the now caseous areas, but often it is possible to establish the type of proliferative or exudative response prior to caseation and to observe the number and location of acid-fast organisms. The destructive and caseous bronchial tuberculosis and the course of the bronchi in caseous nodules can also be readily identified. Sections of the larger bronchi and hilar nodes were made routinely. In some of the cases the position and relationship of the different pulmonary lesions were illustrated semi-diagrammatically. These reconstructions were based upon very thin sections of the pulmonary tissue guided by the dissecting microscope and by selected microsections.

In each case a reconstruction of the evolution of the pulmonary tuberculosis was based upon: (*1*) the symptomatology of the patient, (*2*) the changing quantity of acid-fast organisms in the sputum, (*3*) the course of the lesions demonstrated in frequent chest roentgenograms, and (*4*) the study of pathologic material. The present report is one phase of the above study, the role of the small as well as the large bronchi in pulmonary tuberculosis.

EVALUATION OF MATERIAL

An accurate study of pulmonary tuberculosis in man should be based upon all forms and severity of morphologic lesions. In a sense, the present material has been "selected" from the more severe cases, since it usually deals with autopsy material on patients who died of tuberculosis or upon surgical resections of lesions not amenable to other forms of therapy such as pneumothorax, phrenemphraxis, or thoracoplasty. Thus, while the cases are not entirely representative of the bulk of pulmonary tuberculosis with minimal disease discovered clinically or only by careful routine autopsies, they are not dissimilar to those requiring institutional and therapeutic management, as shown by the indications for surgical resections listed in table 1. Such indications for resection are comparable to those of other institutions.

The few "mild" cases have been observed as an incidental finding in patients in whom death was due to other diseases or in whom surgical resection was performed for other concomitant diseases or other diagnostic possibilities.

The surgical material has not been obtained from any predominant areas of pulmonary tissue. The 149 partial resections involved the following areas: upper lobe, 79; upper and middle lobes, 7; lower lobe, 6; lower and middle lobes, 37; upper lobe and segment of lower, 11; middle lobe and segment of lower, 1; middle lobe, 3; segment alone, 5. Since the presence of lower lobe disease is one

of the indications for surgery, the ratio of lower to upper lobe disease in the surgical material is much greater than the usual clinical ratio.

The ages of the surgical group, ranging from 9 to 61 years, had the following distribution by decades: first decade, 2; second, 23; third, 74; fourth, 55; fifth, 39; sixth, 5; seventh, 2. The sex and race distribution was as follows: white female, 97; Negro female, 31; white male, 54; Negro male, 18.

In general, therefore, the material of the present study is comparable to that seen in most tuberculous patients with moderately or far advanced pulmonary disease.

TABLE 1

Indications for Resection

	PNEUMONECTOMY	LOBECTOMY
Destroyed lung	30	
Giant cavity and acute disease		23
Thoracoplasty failure		23
Cavity open under pneumothorax		10
Solid lesions		25
Lower lobe disease		42
Bronchial disease	9	8
Bronchopleural fistula	7	
Concomitant bronchiectasis	3	5
Diagnosis in doubt		6
Technical	2	
Miscellaneous		7
Total	51	149

THE LESIONS OF TUBERCULOUS BRONCHITIS

The different morphologic forms of tuberculous bronchitis may be indicated by the following working outline:

- Large bronchi
  - Changes in wall
    - Submucosal tubercles
    - "Tuberculoma" of wall
    - Ulceration
    - Erosion of caseous lymph node
  - Changes in lumen
    - Stenosis
      - Endobronchial disease
      - Peribronchial fibrosis
    - Distortion from extrinsic factors
    - Destruction with collapse of walls
- Small bronchi and bronchioles
  - Dilatation
  - Obstruction
    - Luminal exudate, "plugs"
    - Edema of wall
    - Submucosal tubercles

Fibrosis
Distortion
Obliteration
Caseous destruction
Fibrosis
Lithiasis

The "large" bronchi include the main stem and lobar and segmental branches, while the "small" bronchi are all other more peripheral branches including "medium-sized" bronchi and bronchioles. This arbitrary division is of some practical value since there are differences in the symptomatology, prognostic significance, therapeutic management, and bronchoscopic findings in the two groups. The various classifications of tuberculous bronchitis are determined by the emphasis placed upon ulceration, obstruction, localization, and fibrosis. The outline is a mixture of features of importance in the discussion of bronchial tuberculosis, such as anatomic site, functional effects, and pathologic changes.

Large Bronchi

Early lesion: The earliest and mildest of the bronchial lesions consists of scattered tubercles in the submucosa. There is some mononuclear leukocytic infiltration and edema; mucosal ulceration may or may not be present. As the tubercles increase in number, caseation may occur and ulceration is often observed. In the severe stages, all of the bronchial wall may be replaced by tuberculous granulation tissue. Partial or complete healing is accompanied by fibrosis at the site of the tuberculous granulation tissue or by an increased peribronchial collagenous connective tissue. The area of scarring may range from a narrow band to a long section of the wall. Luminal narrowing or stenosis may be produced by submucosal tubercles with or without mucosal ulceration and by mild to marked scarring of the wall. The mucosal epithelium frequently undergoes metaplasia; there is some evidence that the metaplastic epithelium regenerates even more rapidly than the usual mucosa (2).

Incidence: A relatively high incidence of endobronchial tuberculosis has been found upon routine bronchoscopic examination of patients hospitalized for pulmonary tuberculosis. In the severer forms of pulmonary tuberculosis, such as those generally studied in this and in other series of surgically resected or autopsied cases, the incidence of bronchial disease has usually been approximately 35 to 60 per cent (4–14, table 2). The pathologic diagnoses in these reported series have usually been based upon macroscopic detection with confirmatory microsections, although some investigators have used routine microscopic examination. Most of the studies have been concerned with tracheobronchitis and, whenever possible, the values reported in the various series have been used to depict only the incidence of the bronchial disease. The incidence of tracheobronchial tuberculosis in various autopsy series prior to 1929 has been reviewed by Minkovsky (3).

Relationship to parenchymal disease: Bronchial tuberculosis appears to be more frequent in the female sex, and is generally considered to be secondary to paren-

chymal disease. Meissner (7) concluded that the primary parenchymal focus may be of varying size and age and not necessarily a cavity, although 20 of his 31 cases of endobronchial tuberculosis were associated with pulmonary tuberculous cavitation. Sweany and Behm (9) observed that the incidence of endobronchial disease increased with the severity of parenchymal disease, but found no definite relationship of the bronchial disease to the presence or absence of cavitation. Salkin, Cadden, and Edson (14) observed clinically that endobronchial disease occurred three times as frequently with pulmonary cavitation and with sputum containing acid-fast bacilli as in the absence of cavitation with no acid-fast bacilli in the sputum. These writers noted that endobronchial tuberculosis was approximately three times as frequent in disease of the lower

TABLE 2

Endobronchial Disease in Pulmonary Tuberculosis

Twelve Series Collected from Literature

AUTHOR	HOSPITALIZED PATIENTS WITH PULMONARY TUBERCULOSIS	RESECTIONS	AUTOPSIES	PER CENT INCIDENCE OF ENDOBRONCHIAL DISEASE			
				Bronchoscopic	Pathologic	Female	Male
McIndoe *et al.* (4)	272			11.0			
Warren *et al.* (5)	90			13.3			
MacRae *et al.* (6)	335			18.5		28.0	7.0
Meissner (7)		60		25.0	51.7		
Buckles and Neptune (8)		58		14.0	66.6	76.6	55.5
Sweany and Behm (9)			667		56.5	67.9	47.4
Wilbur (10)			500		35.4		
Flance and Wheeler (11)			285		3.2		
Huang (12)			115		39.1		
Bugher *et al.* (13)			122		33.6	39.8	29.9
Salkin *et al.* (14)	622			15.5		16.0	14.9
Salkin *et al.* (14)			125		40.0	48.0	31.0

as compared with disease of the upper lobes; in 79 per cent of their cases the tracheobronchitis improved when the parenchymal disease improved.

Pathogenesis: There are several concepts for the pathogenesis of tuberculous bronchitis: (*1*) implantation of tubercle bacilli in the bronchial mucosa or in the crypts of the mucous glands (9, 12, 13, 15); (*2*) spread along a lymphatic of the bronchial wall (7, 16); (*3*) continuous submucosal extension (16, 17); (*4*) extension from contiguous lymph node or contiguous tuberculous pneumonia (16) via lymphatics to extracartilagenous bronchial mucous glands thence to submucosa.

Lymphatic dissemination: The observations in favor of lymphatic dissemination may be summarized as follows:

Tubercles occur frequently in hilar lymph nodes (7), indicating a lymphatic extension of parenchymal tuberculosis. A major lymphatic pathway (16) is present in the adventitial portion of the bronchial wall. When the endobronchial disease is present the bronchus

is involved all the way to the parenchymal focus (7), although various areas may be more severe. The most striking characteristic of tuberculosis of the major bronchi is the tendency to affect the mucous glands (16), the structures nearest the adventitial lymphatic pathway. Extensive endobronchial disease may have an intact mucosa (7, 16); and the bronchus, a few centimeters from an active, excavating lesion, may have an intact mucosa (16), suggesting that implantation is not a significant factor. Finally, endobronchial disease may occur without an open parenchymal lesion.

Implantation theory: In favor of the implantation theory are the following observations:

The great majority of tuberculous bronchial lesions are associated with cavitation and sputum positive for tubercle bacilli. The most severe bronchial disease is usually nearest the parenchymal focus. The most common site for extrapulmonary tuberculosis in the presence of endobronchial disease is in the intestine where lesions are also produced by implantation (12). The incidence of bronchial involvement is higher in the lower lobe where drainage of sputum is less effective (14). The posterior part of the trachea is most frequently involved, and to approximately the same degree at all levels in fatal cases, suggesting the occurrence of implantation in the recumbent patient (13). The site of implantation may be much smaller than the subsequent submucosal reaction; the mucosa may heal very rapidly over the persistent submucosal lesion.

From the writers' studies it appears that tuberculosis of the larger bronchi may arise by all the routes named above, but that the submucosal extension is probably the most common. This may be by lymphatics or tissue interstices in much the same manner as the spread of carcinomas. The initial bronchial disease could thus arise by implantation from a parenchymal lesion with its adjoining bronchus and from extension of adjacent disease, and then spread along the submucosa. It should be noted that, even when ulcerative tuberculous bronchitis is present, the hilar nodes often contain only noncaseating tubercles; conversely, caseation necrosis in hilar nodes may be sometimes observed without evidence of endobronchial tuberculosis.

Tuberculous bronchitis without associated parenchymal disease: A marked tuberculous bronchitis unassociated with any evident parenchymal lesion may occur (18–25). In the writers' series, 4 such cases have been observed clinically, and 3 in the surgical material. Several other instances belonging in this category have been studied but, since a "parenchymal focus" was present, even though it was

FIG. 1. Examples of bronchial tuberculosis

a. The ostium of a large bronchus is completely obliterated. Distal to this obstruction the bronchi were distended with mucoid, slightly purulent material.

b. A small peripheral bronchus is distended and filled with mucoid material; the lumen is obliterated both proximally and distally. Also present are a caseonodular lesion, several caseous, destroyed small bronchi, and some emphysema.

c. Several centrally located caseous lesions are associated with bronchi and early excavation. The peripheral bronchi are destroyed and replaced by caseation necrosis. (×2)

d. At the periphery of a lung a small bronchus is distorted, while in the central part of the atelectatic secondary pulmonary lobules the bronchioles are destroyed and their luminal sites filled with caseous material. Combined collagen, reticulin, and elastic tissue stain. (×3)

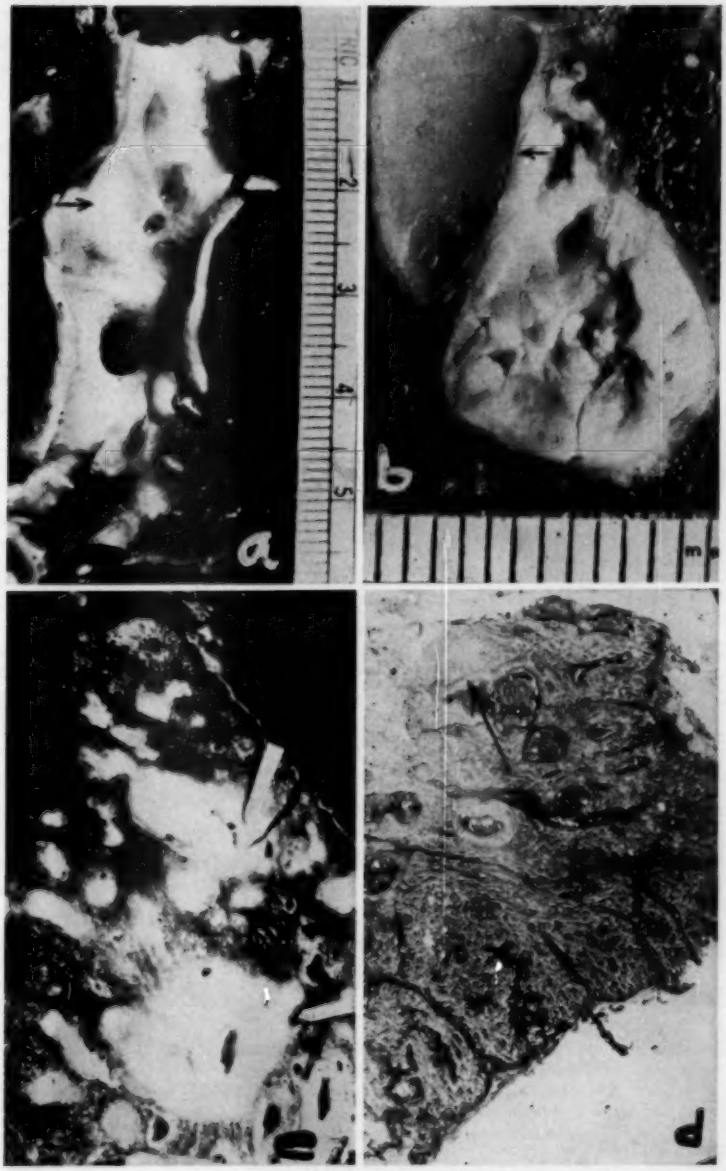


FIG. 1.

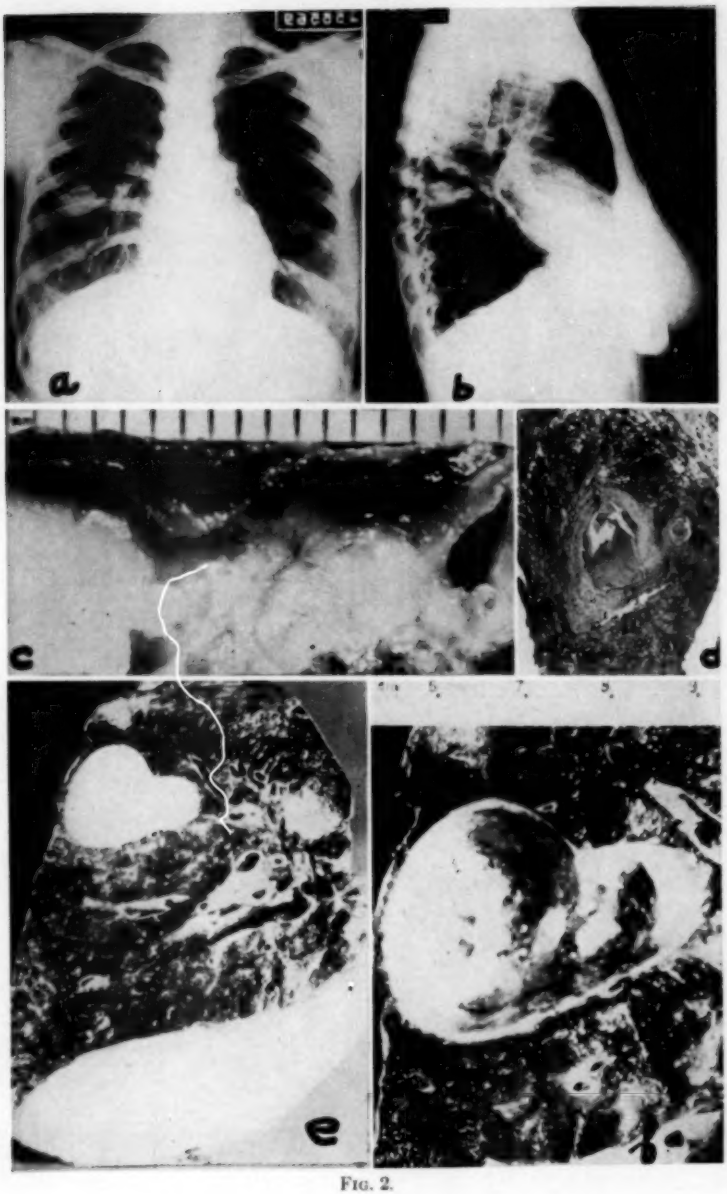


FIG. 2.

a destructive lesion of a peripheral bronchus and probably "secondary" to the proximal bronchial disease, they have not been included. In one instance (figure 1a), only the ostium of a segmental bronchus was obliterated, while mild tuberculous bronchiectasis was found distally. In another case (figure 2) only the first few millimeters of a segmental bronchus were involved in an ulcerative stenosing tuberculous process, while the branches of this segment were greatly dilated. This form of tuberculous bronchial stenosis is sufficiently characteristic to be labeled "ostial stenosis" of segmental bronchus with distal bronchiectasis. Why this short section of the bronchial wall should be involved is difficult to understand unless a small lymph node or lymphoid aggregate at the bronchial bifurcation might have become the site of a tuberculous lesion either from a remote lesion in a retrograde manner, or from a parenchymal lesion now resolved, completely healed, or not observed. The encircling ring of cartilage and connective tissue at the bronchial ostium may predispose to such inflammatory stenosis.

Tuberculoma of bronchial wall: "Tuberculomas" of the bronchial wall have been described in children (26). Some may represent the parenchymal focus of a primary complex; some, the extension or herniation of an involved lymph node; and others, a focal "hyperplastic" lesion of the bronchial wall. Whatever the origin, the "tuberculoma" bulges into the bronchial wall occluding it to some degree and producing such complications as emphysema, atelectasis, and bronchiectasis. The writers have seen only one such case clinically. A slightly polypoid mass protruded into, and obstructed, the upper lobe bronchus of an eight-year-old child. Biopsy of this lesion revealed tuberculous granulation tissue covered by intact mucosa. It could not definitely be established whether the lesion had occurred within a lymph node which then bulged into the lumen of the bronchus or was a conglomerate mass of submucosal tubercles. In 1942 Jones, Rafferty, and Willis (27) presented cases of primary tuberculosis in children and discussed earlier reports (28–33) which demonstrated that bronchial obstruction was an important factor in the production of the roentgenographic pulmonary consolidation termed "epituberculosis" and "hilar flare." Of 716 children hospitalized for pulmonary tuberculsois, 85 (12 per cent) had such roentgenographic evidence of bronchial obstruction. Bronchoscopic examination was performed in 42 of these patients, and in 31 (74 per cent) bronchial disease or distortion was found. Such bronchial changes were due to the pressure from enlarged hilar nodes or the apparent extension of the disease from the adjacent nodes to the bronchial wall, producing tuberculoma or ulceration. In 1950 a follow-up report (34) was

FIG. 2. Marked segmental bronchiectasis from ostial disease

A survey roentgenogram of a 26-year-old white female disclosed a solid lesion in the upper part of the right lower lobe. This lesion increased in size under several months of artificial pneumothorax; no acid-fast organisms were found in the sputum and no changes were observed upon bronchoscopy. The pneumothorax was discontinued (a and b) and the lower lobe was resected. The ostium of a segmental bronchus was completely obliterated by ulcerative and fibrosing tuberculosis (c). The proximal centimeter of this bronchus was narrowed and its lumen filled with caseous material (d, (×4)). The bronchi of this segment are markedly distended by mucoid, slightly purulent material (e) which is easily removed revealing an intact mucosa (f).

made on 34 such patients in whom bronchograms were performed after the roentgenographic clearing of the pulmonary lesions and after a mean interval of three and one-half years. Definite bronchiectasis was found in 24 patients (70.6 per cent). The bronchiectasis conformed to the segmental structure of the tracheobronchial tree and was due to bronchial obstruction at the root. These authors also found that bronchiectasis occurs in approximately 50 per cent of the cases of fatal reinfection tuberculosis. As would be expected, this percentage is somewhat higher than that observed in the less severe cases of tuberculosis in the surgical material of the present series (table 3).

Distortion of bronchi: Kinking and distortion of the bronchi are usually associated with changes in the adjoining pulmonary tissue such as fibrosis, atelec-

TABLE 3

Bronchial Tuberculosis in the 200 Resected Lungs, Lobes, and Segments

TYPE OF PULMONARY TUBERCULOSIS	NUMBER OF CASES	LARGE BRONCHI				SMALL BRONCHI*			
		Submucosal tubercles	Ulcerative	Ulcerostenosis	Fibrostenosis	Segmental ectasia	Focal ectasia	Destructive	Lithiasis
Large caseonodular lesion ("tuberculoma")	6	3	2			2	2	4	
Multiple caseonodular lesions									
Without excavation	34	17	12	7	15	10	7	18	1
With excavation	30	19	18	7	6	6	6	22	2
Cavities									
With no or few caseonodular lesions	35	25	15	13	17	1	9	22	
With many caseonodular lesions	90	73	41	27	18	17	31	70	5
Caseous pneumonia	2	2	2	1				2	
Bronchial disease only	3	3	2	2	1	3	3	2	

* The small bronchi incorporated in the caseous nodules have not been included.

tasis, or induced collapse. A flaccid bronchial wall sometimes results from destructive changes in the bronchial cartilages. In this situation, expiratory collapse of bronchial walls may be seen by use of the bronchoscope.

Small Bronchi

From the semidiagrammatic reconstructions in figures 3, 4, and 5, it may be observed that pulmonary tuberculosis often appears as nodular "tubers" connected to both proximal and distal bronchial "roots." The proximal or larger bronchi are frequently stenosed while the distal or smaller bronchi are occasionally dilated but more often destroyed by tuberculous disease. Accompanying this peripheral bronchial disease will be found atelectasis (figure 1d) and varying degrees of fibrosis, plasma exudation and alveolar macrophage accumulation, and scattered tubercles. In spite of reports to the contrary, pyogenic, nontuber-

culous responses are unusual, and nontuberculous bronchopneumonia is encountered with great rarity. This phenomenon is not entirely attributable to the selection of afebrile cases for resection. If the periphery of the solid or excavated caseous parenchymal lesion does not abut upon the pleural surface, the peripheral bronchial disease is nearly always more severe than the proximal. It is to be expected that the histologic changes of the smaller and larger bronchi would be similar but more severe in the smaller bronchi. In some bronchi the submucosal

FIG. 3. This semidiagrammatic reconstruction of the lesions in a surgically resected right upper lobe demonstrates the occurrence of caseonodular "tubers" along the proximal and distal bronchial "roots." The caseonodular lesions are beginning to excavate; there is caseous destruction of the peripheral bronchi although one is distended and filled with mucopurulent exudate. Focal ectasia is seen in a patent peripheral bronchus. The larger or proximal bronchi have thickened walls and narrowed lumina.

tubercles stenose and distort the lumen (figure 1b), while in other bronchi and bronchioles mucofibrinopurulent exudate and caseous material fill the lumen and destroy the mucosa and the submucosa with the formation of a few or no tubercles. A small bronchus proximal to a small caseonodular lesion may show either or both of these two changes. These diseased small bronchi may heal with short or long segments of complete fibrosis and obliterated lumen. The formation of concretions is especially apt to occur in the older lesions where some dilatation of the lumina has occurred and where copious fibrinopurulent and even caseous exudate has accumulated. It is not uncommon to see these little irregular

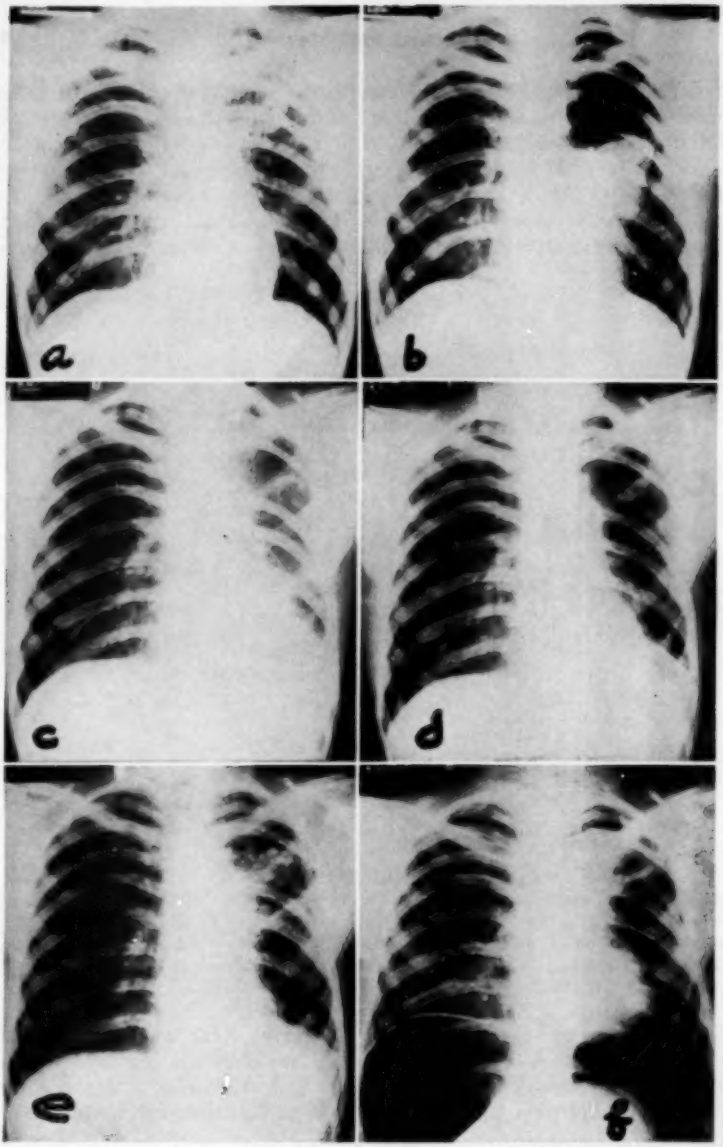


FIG. 4. The series of roentgenograms on this 18-year-old white male reveals the original disease in the left upper lobe (a) which appears as a solid mass upon artificial pneumothorax (b). Several months later the re-expanded upper lobe was resected but new disease appeared in the left lower lobe four months later (c) and gradually progressed six months (d), eight months (e), and ten months (f) postoperatively, with cavitation increasing under the pneumoperitoneum. Figure 5 presents the reconstruction of this left lower lobe.

concretions located in small rounded dilatations of small bronchi, the lumina of which are stenotic or obliterated proximally and distally.

Proximal obstruction of the bronchial tree, either by a caseonodular lesion or by ostial or mural stenosis, appears to play a prominent role in the development of peripheral bronchial disease. This applies especially to the dilated peripheral

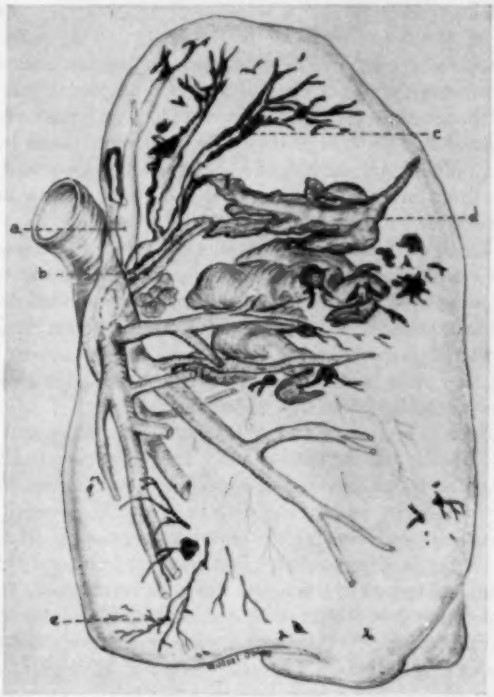


FIG. 5. The semidiagrammatic reconstruction of the lesions in the left lower lobe (see figure 4). The posterior bronchus is stenosed proximally and dilated distally (a) with caseous destruction of the small peripheral bronchi. Another bronchus is markedly stenosed (b). Other bronchi in the upper part of this lobe are the site of marked ulceration and focal ectasia (c). The irregular cavity (d) is associated with caseonodular lesions behind it and is surrounded by marked fibrosis. There are small caseous-destructive bronchial lesions in the lower part of the lobe (e).

bronchi with destructive tuberculous ulceration of their walls. The focal ostial stenosis or obliteration tends to produce more dilatation than destruction of the bronchi. If such stenosis were to occur in a growing individual, the bronchus at the healed but stenotic area might fail to increase in caliber with the increased growth of the body and its viscera. Thus, a progressive, though relative, stenosis might result and the obstructive and infective processes would tend to aggravate the segmental or lobar bronchiectasis.

ROLE OF BRONCHI IN PATHOGENESIS OF PULMONARY TUBERCULOSIS

The frequent resemblance of the lesions of pulmonary tuberculosis to "tubers" along the proximal and distal bronchial "roots" dramatizes the pathogenetic concept that pulmonary tuberculosis is a chronic, localizing, and recurring bronchopneumonia characterized by the formation of microscopic "tubercles" which often coalesce and undergo a peculiar necrosis termed "caseous." Considered as one of the tissue reactions of the host, not dissimilar to other inflammatory reactions, the aura of mystery surrounding tuberculosis disappears. Like other pneumonias, acute or chronic, the infecting organisms enter via the airways and, although they may spread by the blood or lymph vessels, they are most often disseminated to other parts of the pulmonary tissue by the bronchi. Like suppurative pulmonary disease, the involvement is frequently of a lobular form and may drain or excavate its necrotic contents into a bronchus, thus forming an abscess or cavity.

The general host reaction and the morphologic pattern of disease is modified by the metabolic features of the infecting organism. The hardy tubercle bacilli are aerobic. The aerated cavity, lined by tuberculous granulation tissue and coated with plasma proteins, leukocytic and erythrocytic debris, is an excellent site for the growth of these organisms. Great numbers may appear in the sputum or be aspirated into other parts of the lung. A hemorrhage originating from the cavity may spread the bacilli to new pulmonary sites.

Thus, the bronchial lumina provide the avenue of entrance and the avenue of spread for the tubercle bacilli, both distally as well as proximally, from areas of solid or excavated nodular disease of reinfection tuberculosis. In addition, the bronchial wall lymphatics and interstices afford another avenue for spread of the bacilli, frequently producing mild or severe lesions therein. If mucosal ulceration accompanies the proliferation of submucosal and mucosal tubercles, a new nidus for the luminal spread of the bacilli has been established. The tuberculous granulation tissue may by its bulk or by constricting fibrosis produce a stenosis. Bronchial obstruction by either distortion, compression, or stenosis may lead to distal atelectasis or to distention with the "retention of secretions" in bronchi. If a marked stenosis involves a large bronchus to a lobe or segment which is free of significant parenchymal tuberculosis, bronchiectasis with or without destructive peripheral tuberculous bronchitis may result. If the stenosis involves a large bronchus with parenchymal disease distally, such obstruction may precipitate the excavation of a solid lesion, the distention of a cavity, interference with the collapse of such cavities, and even disseminate the infecting bacilli to tissue distal to either the stenosis or to the major parenchymal disease (figure 6). On the other hand, the proximal bronchial disease may aid in cavity closure and clearing of parenchymal disease (14, 35).

In 1929 Loeschcke (36), in an excellent paper, emphasized the role of the small bronchi and described the spread of apical tuberculosis along the bronchi to adjacent areas. The reconstructions of the lesions of pulmonary tuberculosis by the writers support such views. Any lesion not abutting upon the visceral pleura can spread distally via lumina or walls of bronchi, thus extending through

the ever widening area of the bronchial tree until the pleural surface is reached (figures 3, 6). This peripheral spread might be enhanced by increased respiratory movements and inhibited by the diminution of ventilatory activity through bed rest or collapse therapy. The distal destructive bronchial disease with broad areas

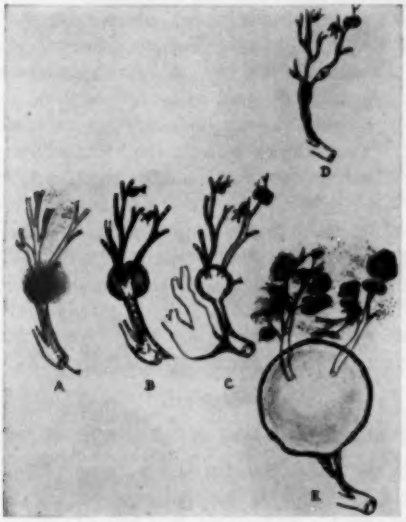


FIG. 6. Effects of proximal bronchial disease upon a nonperipheral caseous lesion and distal destructive bronchial disease.

A. Tubercle bacilli are aspirated and an area of caseation results.

B. The discrete caseonodular lesion develops, begins to excavate; distally the peripheral bronchi are destroyed and the luminal site filled with caseous material and/or exudate; there is accompanying atelectasis; proximally the disease may spread to the bronchial walls by direct submucosal extension or by implantation.

C. Stenosis near the orifice of the bronchus may produce segmental bronchiectasis. Such distended bronchi are usually filled by thick mucoid material mixed with variable quantities of exudate as in figure 2. The excavation of the caseous lesion advances and the excavation may extend to the caseous bronchi distally.

D. Stenosis of the proximal bronchus may lead to cavity refilling with exudate or to actual healing. The peripheral atelectasis increases. Peripheral bronchi and bronchioles may be completely obliterated or focally distended. Small concretions may occur at their luminal sites.

E. The cavity may "balloon" with air or various fluid and solid materials. The peripheral disease may advance with or without this change in the cavity.

of atelectasis over those tuberculous lesions away from the pleural surface would seem to be more important in the "selective collapse" of the diseased area than the changes in proximal bronchi. Proximal bronchial disease may be important in the closure of cavities (35, 37) or in the production of a "blocked" cavity (38), in the "ballooning" of cavities, or in the production of emphysema (39). The

presence of such bronchial lesions may possibly account for the failure of some diseased lobes to collapse under thoracoplasty (40).

SUMMARY

The morphologic forms, incidence, and pathogenesis of bronchial tuberculosis are discussed. Lesions of the smaller bronchi are often more numerous and more severe than those of the larger bronchi. Tuberculosis of the large bronchi occurs most frequently in association with cavitation and sputum containing tubercle bacilli, but may occasionally be found without detectable parenchymal lesions.

In pulmonary tuberculosis the bronchi, both large and small, play a most important role, since their walls and especially their lumina serve as major avenues for spread of the disease, not only within a lobe or segment but to other sites as well.

Reconstructions of pulmonary and bronchial disease indicate that nodular or cavity parenchymal lesions frequently occur like "tubers" along both proximal and distal bronchial "roots." Distal or peripheral bronchial lesions result in atelectasis and may lead to the spread of parenchymal lesions which do not abut upon the pleura. Lesions of the proximal or larger bronchi may have a favorable or unfavorable influence upon the parenchymal disease distal thereto.

SUMARIO

El Papel de los Bronquios en la Tuberculosis Pulmonar

En este repaso de las formas, incidencia y patogenia de la tuberculosis bronquial, señálase que las lesiones de los bronquios pequeños son a menudo más numerosas y graves que las de los mayores. La tuberculosis de los bronquios grandes sobreviene más frecuentemente en asociación con cavernas y esputo poblado de bacilos tuberculosos, pero puede a veces existir sin lesiones descubribles del parénquima.

En la tuberculosis pulmonar, los bronquios, tanto grandes cuanto pequeños, desempeñan un papel de lo más importante, visto que las paredes y sobre todo la luz de los mismos constituyen grandes avenidas para la propagación de la dolencia, no sólo dentro de un lóbulo o segmento sino también a otros sitios.

Las reconstrucciones de la afección pulmonar y bronquial indican que las lesiones parenquimatosas, ya ganglionares o cavernosas, toman frecuentemente forma de "tubérculos" a lo largo de las "raíces" tanto proximales como distales de los bronquios. Las lesiones bronquiales distales o periféricas culminan en atelectasia y pueden conducir a la difusión de lesiones parenquimatosas que no tocan la pleura. Las lesiones de los bronquios proximales o mayores pueden ejercer efecto favorable o desfavorable sobre la enfermedad parenquimática distal a las mismas.

RESUME

Le rôle des bronches dans la tuberculose pulmonaire

Les aspects morphologiques, l'incidence et la pathogénèse de la tuberculose bronchique sont étudiés. Les lésions des petites bronches sont souvent plus

nombreuses et plus graves que celles des bronches de plus gros calibre. La tuberculose des grosses bronches se produit plus fréquemment; elle est associée à la présence de cavernes et de crachats contenant le bacille tuberculeux, mais elle s'observe parfois sans qu'on puisse déceler de lésions du parenchyme.

Dans la tuberculose pulmonaire, les bronches, qu'elles soient grosses ou petites, jouent un rôle des plus importants car leurs parois et plus encore leur lumière sont des voies importantes de diffusion de la maladie, non seulement au niveau d'un lobe ou d'un segment du poumon, mais aussi vers d'autres régions.

L'étude des lésions pulmonaires et bronchiques indique que les lésions parenchymateuses cavitaires ou nodulaires se développent comme des tubercules le long des "racines" bronchiques tant proximales que distales. Des lésions bronchiques distales ou périphériques déterminent l'atélectasie et peuvent causer l'invasion du parenchyme sans contact avec la plèvre. Les lésions des bronches proximales, ou grosses bronches, peuvent avoir une influence favorable ou défavorable sur la lésion parenchymateuse distale qu'elles desservent.

REFERENCES

(1) Pinner, M.: Pulmonary Tuberculosis in the Adult: Its Fundamental Aspects, Charles C Thomas, Springfield, Illinois, 1945.

(2) Condon, W. B.: Regeneration of tracheal and bronchial epithelium, J. Thoracic Surg., 1941, *11*, 333.

(3) Minkovsky, A.: Tuberculosis of the trachea, Laryngoscope, 1929, *39*, 819.

(4) McIndoe, R. B., Steele, J. D., Sampson, P. C., Anderson, R. S., and Leslie, G. L.: Routine bronchoscopy in patients with active pulmonary tuberculosis, Am. Rev. Tubere., 1939, *39*, 617.

(5) Warren, W., Hammond, A. E., and Tuttle, W. M.: The diagnosis and treatment of tuberculous tracheobronchitis, Am. Rev. Tuberc., 1938, *37*, 315.

(6) MacRae, D. M., Hiltz, J. E., and Quinlan, J. J.: Bronchoscopy in a sanatorium: A review of 522 consecutive bronchoscopies, Am. Rev. Tubere., 1950, *61*, 355.

(7) Meissner, W. A.: Surgical pathology of endobronchial tuberculosis, Dis. of Chest, 1945, *11*, 1.

(8) Buckles, M. G., and Neptune, W. B.: Tuberculous bronchitis in pulmonary resection, Am. Rev. Tuberc., 1950, *61*, 185.

(9) Sweany, H. C., and Behm, H.: Tuberculosis of the trachea and major bronchi, Dis. of Chest, 1948, *14*, 1.

(10) Wilber, G. H.: Tuberculosis of the trachea and major bronchi, Quart. Bull., Sea View Hosp., 1942, *7*, 361.

(11) Flance, I. J., and Wheeler, P. A.: Post-mortem incidence of tuberculous tracheobronchitis, Am. Rev. Tubere., 1939, *39*, 633.

(12) Huang, C. S.: Tuberculous tracheobronchitis: A pathologic study, Am. Rev. Tuberc., 1943, *47*, 500.

(13) Bugher, J. C., Littig, J., and Culp, J. E.: Tuberculous tracheobronchitis, Am. J. M. Sc., 1936, *193*, 515.

(14) Salkin, D., Cadden, A. V., and Edson, R. C.: The natural history of tuberculous tracheobronchitis, Am. Rev. Tubere., 1943, *47*, 351.

(15) Louis, P. C. A.: Research on Phthisis, C. & J. Adlard, London, ed. 2, 1844 (quoted by Salkin, Cadden, and Edson).

(16) Reichle, H. S., and Frost, T. T.: Tuberculosis of the major bronchi, Am. J. Path., 1934, *10*, 651.

(17) Epstein, H. H., and Ornstein, G. G.: Tuberculosis of the trachea and main bronchi, Quart. Bull., Sea View Hosp., 1936, *1*, 272.

(18) Ornstein, G. G., and Epstein, I. G.: Tuberculosis of the major bronchi with little or no manifest pulmonary tuberculosis, Quart. Bull., Sea View Hosp., 1938, *3*, 109.

(19) Chamberlain, J. M., and Gordon, J.: Treatment of endobronchial tuberculosis, J. Thoracic Surg., 1942, *11*, 292.

(20) Sampson, P. C.: Tuberculous tracheobronchitis: The role of bronchoscopy, Am. Rev. Tubere., 1936, *34*, 671.

(21) Steiner, P. M.: La forme stenosante de la tuberculose apparemment primitive des bronches souches, Rev. de la tubere., 1946, *10*, 159.

(22) Jacquelin, A., Villanova, P., and Blanchon, P.: La tuberculose et les bronches (Bull. Med., No. 26, *28*, 1941), Abstract, Ann. d'-oto-laryng., 1946, *63*, 491 (quoted by N. Froste).

(23) Myerson, M. C.: Tuberculosis of the trachea and bronchus, J.A.M.A., 1941, *116*, 1611.

(24) Vanduffel, J.: Bronchoscopie en longaandoeningen, Abstract, Excerpta Med., Sec. 11: Oto-Rhino-Laryng, 1949, *2*, 338.

(25) Froste, N.: Bronchoscopy in pulmonary tuberculosis, Acta tubere. Scandinav., 1950, Supplement 28.

(26) Moorhead, R. L.: Tuberculoma of bronchus: Report of case, Ann. Otol., Rhin. & Laryng., 1937, *46*, 755.

(27) Jones, E. M., Rafferty, T. N., and Willis, H. S.: Primary tuberculosis complicated by bronchial tuberculosis with atelectasis (epituberculosis), Am. Rev. Tubere., 1942, *46*, 392.

(28) Morelock, H. V., and Pinchin, A. J. S.: Epituberculosis—a query as to the entity of this condition, Lancet, 1933, *1*, 1114.

(29) Korol, E.: Atelectasis in pulmonary tuberculosis, Am. Rev. Tubere., 1931, *123*, 493.

(30) Macpherson, A. M. C.: Primary tuberculosis of the lung in children, Brit. J. Tubere., 1939, *33*, 79.

(31) Terplan, K.: Anatomical studies on human tuberculosis, Am. Rev. Tubere., supplement, August 1940.

(32) Sanes, S., and Smith, W. S.: Massive pulmonary atelectasis following bronchial obstruction in tuberculosis, Am. Rev. Tubere., 1937, *36*, 727.

(33) Eloesser, L.: Bronchial stenosis in pulmonary tuberculosis, Am. Rev. Tubere., 1934, *30*, 123.

(34) Jones, E. M., Peck, W. M., Woodruff, C. E., and Willis, H. S.: Relationships between tuberculosis and bronchiectasis: A study of clinical and of post-mortem material, Am. Rev. Tubere., 1950, *61*, 387.

(35) Corylos, P.: Pathologic physiology and mechanics of selective collapse, Quart. Bull., Sea View Hosp., 1937, *2*, 244.

(36) Loeschcke, H.: Development, cicatrization and reactivation of pulmonary tuberculosis in adults, Beitr. z. Klin. Tuberk., 1938, *68*, 251.

(37) Pagel, W., and Simmonds, F. A. H.: Cavity healing and bronchial occlusion, Am. J. M. Sc., 1942, *203*, 177.

(38) Salkin, D., Cadden, A. V., and McIndoe, R. M.: The blocked pulmonary cavity: An anatomical, roentgenological and clinical study, Am. Rev. Tubere., 1936, *34*, 634.

(39) Dahlstedt, H.: Endobronkiell diagnostik och behandling vid lungoch bronkialtuberkulos, Nord. med., 1944, *22*, 681 (quoted by N. Froste).

(40) Crafoord, C.: Till bronkialtuberkulosens kirurgiska behandling, Nord. med., 1939, *2*, 1231 (quoted by N. Froste).

BRONCHOGENIC CARCINOMA AS A DIFFERENTIAL DIAGNOSTIC PROBLEM IN PULMONARY DISEASE[1]

III. Peripheral Type: Carcinoma Arising from the Minor Bronchi and Bronchioles

JOHN H. MOYER AND ALFRED J. ACKERMAN

(Received for publication July 17, 1950)

Gross morphologic characteristics and the clinical manifestations which accompany bronchogenic carcinoma of peripheral origin have led to its classification as a form distinct from that arising in the major bronchi. However, there is no oncologic difference between the two. Although the central type is about three times as common as the peripheral variety (1), it is apparently less malignant (2). This may be due to a higher incidence of anaplastic and glandular tumors in the latter (3). More likely, it is a result of late clinical recognition.

A carcinoma arising in the periphery may occasionally remain confined to the respiratory passages and alveoli without eroding the involved bronchus. This type has been termed "alveolar cell carcinoma." More frequently, these peripheral tumors erode the bronchus early in the course of the disease and then continue to grow expansively within the pulmonary parenchyma, maintaining a well demarcated border. The circumscribed peripheral lesions are thus produced.

Peripheral Circumscribed Bronchogenic Carcinoma

Peripheral circumscribed carcinomas are usually of a homogeneous, soft tissue density. They are spherical in shape, and even though increasing in size they frequently maintain a sharp contour. Occasionally they do not maintain this sharp demarcation, but instead may extend along the peribronchial lymphatics, producing a "lymphangitic carcinomatous extension."

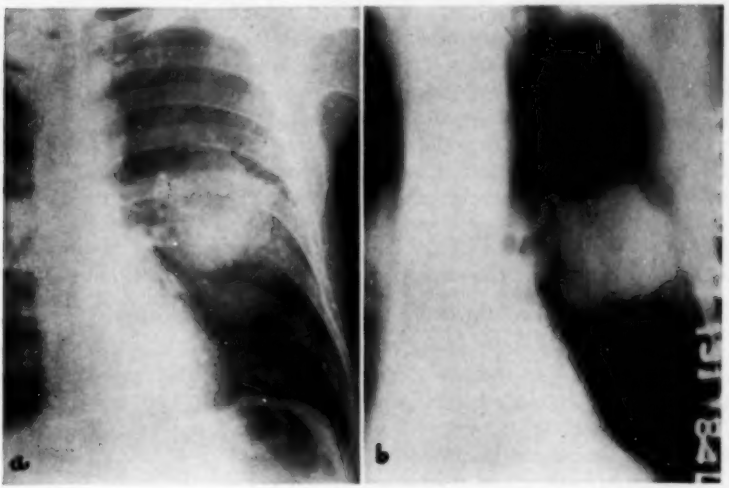
Clinical symptoms of any magnitude are not found early in the disease due to the absence of occlusion of large bronchi. The mediastinal structures are usually unaffected, since displacement due to atelectasis or pressure is extremely rare. Because of this relatively common "clinical silence," the disease does not come to the attention of the patient or the doctor before metastases to distant organs have occurred. Many "brain tumors" are due to metastases from an unrecognized primary carcinoma of the lung. Even when suspected, a specific diagnosis of peripheral-type bronchial carcinoma is frequently difficult without surgical assistance. The lesions are not accessible to bronchoscopy. Bronchography is not always reliable, particularly when the mass is still small. At times, body-section roentgenography may add valuable information, but frequently the results of this procedure are also far from conclusive. It is believed that, in cases in which circumscribed peripheral densities of unknown origin are observed, an exploratory thoracotomy is indicated. This is especially true when the usual studies concerning specific inflammatory diseases yield no information, and when there is no indication of vascular disease in patients who previously had normal findings on roentgenographic examination of the chest.

[1] From the Baylor University College of Medicine, Houston, Texas.

Peripheral circumscribed carcinoma is frequently quite difficult to differentiate from pulmonary vascular and chronic inflammatory lesions if clinical manifestations and conventional roentgenographic studies alone are used for evaluation. Collateral studies, however, may add enough additional information to reach a diagnostic conclusion. The following cases exemplify some of these possibilities:

Case 24. A 39-year-old white male was admitted because of weakness, headache, irritability, and hypertension. There were no symptoms referable to the chest.

Routine roentgenographic examination of the chest showed a fairly well defined, round area of increased density in the periphery of the lung at the level of the third left intercostal



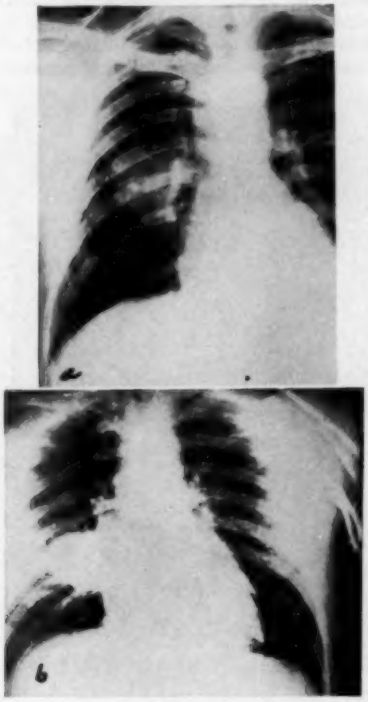
Case 24

FIG. 24. (a). Circumscribed, homogeneous, dense infiltration in the third and fourth left interspaces due to bronchogenic carcinoma.

(b). Laminagram. The upper and lower lobe bronchi are normal. The tumor has arisen in the lingula and is extending toward the left upper lobe bronchus.

space anteriorly. Because of temporary regression, the density was thought to represent an inflammatory infiltration. Further roentgenographic observation was advised to determine the progress of the lesion. However, the patient did not return to the clinic for eighteen months. Physical examination at that time revealed marked clubbing of the fingers and toes. Many crackling rales were heard in the left upper chest and relative dullness to percussion was present over the same area. Roentgenographic examination at the time of the last admission showed an enlargement of the previously observed infiltration which maintained its round shape and well-defined contour without evidence of "radiation" into the adjacent parenchyma. Body-section roentgenograms confirmed the presence of a homogeneous mass originating near the divisional bronchi of the lingula. A diagnosis of *peripheral bronchogenic carcinoma* was made. At surgery a well-circumscribed, large, bronchogenic carcinoma was found in the lingula with direct extension to the pleura and metastases to the mediastinum.

Although in this instance there was nothing distinctive in the laboratory, clinical, or conventional roentgenographic studies, laminagraphic studies revealed the neoplastic nature of the disease. Surgery, although unsuccessful, was undertaken with more assurance. Laminagraphy may not only help in the diagnosis of this peripheral type of carcinoma, but at the same time may aid in



Case 25

FIG. 25. (a). Pulmonary arteriovenous fistula located in the apex of the right lower lobe. (b). Cardioangiogram. The fistula is filled with diodrast, thus confirming the vascular nature of the opacity.

differentiating pathologic entities which present similar densities on the routine chest roentgenograms.

Case 25. A 29-year-old white male, one of a family with proved hereditary hemorrhagic telangiectases, was separated from military service three years previously because of polycythemia and a "benign lung tumor." For six months prior to admission the patient had noticed increasing dyspnea on exertion, palpitation, weakness, cyanosis, clubbing of the fingers, and recurrent bleeding from telangiectatic areas on the face, lips, and mucous mem-

branes of the mouth and pharynx. A diastolic murmur was heard over the pulmonic area and in the interscapular area posteriorly.

Roentgenographic examination of the chest revealed a circular shadow of increased density in the right lower lung field which lay near the apex of the right lower lobe. The inferior-lateral margin of this density showed a double convex contour. On fluoroscopy a slight pulsation of the pulmonary opacity was observed, and the oblique and lateral views showed a large vessel extending from the hilum and merging with the described shadow. The Valsalva test showed a slight decrease, and the Mueller test showed an increase, in size of the pulsating mass. Cardioangiography confirmed the vascular nature of the "tumor", *pulmonary arteriovenous fistula*, and thus disproved the original diagnosis of a benign pulmonary neoplasm. These observations were confirmed surgically. Although segmental resection was

FIG. 26. Case 26. Circumscribed dense infiltration at the base of the left lung anteriorl y A diagnosis of coccidioidomycosis was made on the basis of history, positive skin test, and pulmonary calcification noted on laminagraphic studies.

contemplated, numerous small fistulas were found throughout the right lung. A pneumonectomy was performed, and convalescence was uneventful.

In this instance the possible vascular nature of the pulmonary opacity was suggested by the history of telangiectasis of the skin and mucous membranes, the mid-scapular cardiovascular murmur, the cyanosis, and the polycythemia. Fluoroscopic examination revealed a decrease in the size of the mass when the intrathoracic pressure was increased. The diagnosis of pulmonary arteriovenous fistula was firmly established by the findings on cardioangiography. A previous erroneous diagnosis of pulmonary neoplasm was thus corrected.

Case 26. A 51-year-old white male was admitted for study because of a pulmonary opacity noted on a "survey examination." Although asymptomatic at this time, he gave a history

of severe respiratory infection two years previously, which had lasted approximately three weeks and was accompanied by nodular erythematous lesions on both legs. On the present admission the skin did not react to tuberculin; the coccidioidin skin test was positive.

The chest roentgenogram showed a circumscribed oval infiltration in the left lower lobe anteriorly and laterally just above the diaphragm. Laminagraphic studies confirmed the solid nature of the infiltration and revealed calcification which was not visible on the routine chest film. A diagnosis of chronic *pulmonary coccidioidomycosis* was made. Follow-up examination three years later revealed no essential change.

In this instance a diagnostic conclusion could be reached on the basis of history, laboratory findings, and laminagraphic studies. The last named revealed calcification within the lesion that had not been noted previously. This

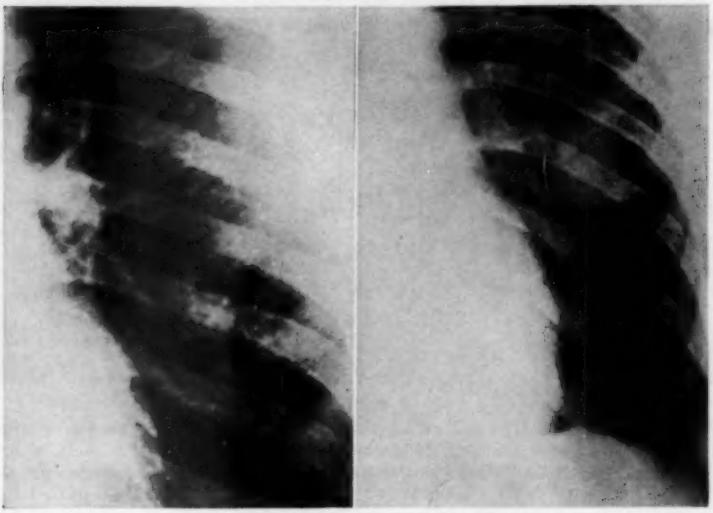


FIG. 27. Case 27 (Left). Infiltration in the second left interspace which proved to be a tuberculoma. This appears quite similar to figures 26, 28, and 29.

FIG. 28. Case 28 (Right). Infiltration in second left interspace which proved to be an area of localized fibrosis, probably a residual manifestation of pneumonia or infarction.

immediately suggested an inflammatory origin of the infiltrate. The history and a positive coccidioidin skin test aided in establishing the probable etiology. Follow-up observations three years subsequently further confirmed the nonmalignant nature of this lesion.

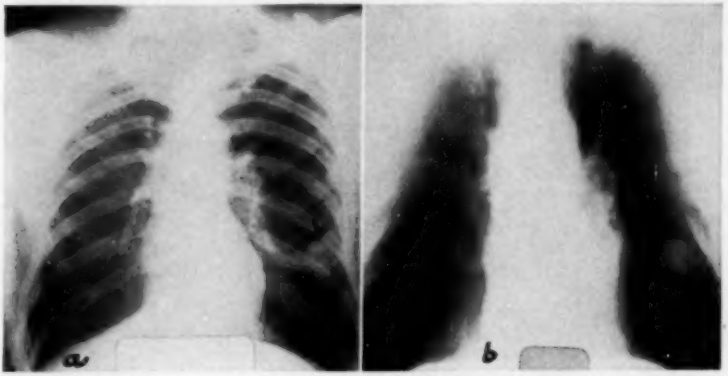
Case 27. A 47-year-old white male was admitted for medical observation because of a pulmonary lesion discovered on a routine roentgenographic examination. Except for a positive tuberculin test, physical examination and laboratory studies were noncontributory. The coccidioidin and histoplasmin skin tests were negative.

Roentgenographic examination of the chest showed a well-defined, round area of increased density near the periphery of the second left intercostal space anteriorly. No calcifications were noted. Bronchoscopy and bronchography showed no definite abnormality of

the bronchial tree. A diagnosis of *tuberculoma* was made. Because the possibility of neoplasm could not definitely be excluded, however, a thoracotomy with segmental lobar resection was performed. Pathologic examination of the resected specimen revealed a *tuberculoma*.

Case 28. A 23-year-old white male was admitted because of three recurrent attacks of severe chest pain during the past two years. Each attack lasted several days. Physical examination and laboratory studies were essentially negative.

Roentgenographic examination revealed a round, sharply outlined opacity in the second left interspace measuring 3 cm. in diameter. Bronchoscopy, laminagraphy, bronchography, and laboratory studies showed no evidence of intrabronchial disease. Pathologic studies after partial resection of the left lower lobe revealed an old, organized, circumscribed fibrotic area which may have been an organized infarct or an *organized pneumonia*. No further conclusions could be drawn.



Case 29

FIG. 29 (a). Circumscribed infiltration in the left lower lobe which proved to be a bronchial adenoma that had undergone malignant degeneration.

(b). Laminagram showing the dense nature of the tumor which has extended along the bronchus.

The two preceding cases (Cases 27 and 28) are examples of chronic inflammatory disease (tuberculoma and an organized pneumonic lesion) which presented no distinctive clinical, laboratory, or roentgenographic manifestations. Other studies were likewise nonrevealing. Exploratory thoracotomy was resorted to as a diagnostic procedure in the absence of sufficient evidence of the non-neoplastic nature of the disease. This procedure is indicated when definite conclusions cannot be reached regarding well-circumscribed, peripheral, pulmonary densities. The finding of calcification in this type of lesion is of considerable value as an assurance of the inflammatory origin of the infiltrate.

Case 29. A 42-year-old white female was studied because of cough and blood-streaked sputum. Physical examination and laboratory studies were nonrevealing.

Roentgenographic examination showed a dense well-circumscribed infiltration in the right mid-lung field. The lateral view proved this infiltration to be in the lower lobe. The laminagram suggested a neoplastic etiology of the infiltration since, at the same time that

it was expanding peripherally, it was apparently also extending along the bronchus. On this basis, a diagnosis of bronchogenic carcinoma was made and the patient was operated upon. The patient is living and well three years after the pneumonectomy was performed.

Pathologic examination of the tumor revealed a *bronchial adenoma* which had apparently undergone malignant degeneration and had extended to the main stem bronchus.

Although bronchial adenomas are usually considered "benign tumors," the above case exemplifies that these tumors are at least potentially malignant. The writers have observed such a tumor in another patient who died with wide-spread metastases following pneumonectomy.

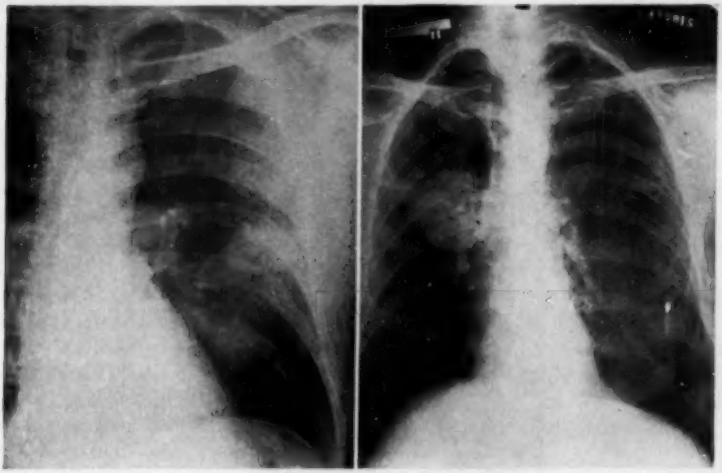


FIG. 30. Case 30 (Left). Circumscribed dense infiltration in the fourth interspace which proved to be metastatic carcinoma. The primary site was in the pancreas.

FIG. 31. Case 31 (Right). Neurofibroma. The extrapulmonary location of this tumor was demonstrated by a diagnostic pneumothorax.

Solitary metastatic carcinoma of the lung may also present roentgenographic changes which closely resemble peripheral-type bronchogenic carcinoma. If a primary site is not in evidence, a working diagnosis of bronchogenic carcinoma is in order and thoracotomy is indicated.

Case 30. A 38-year-old white male was admitted because of cough and chest pain. A roentgenogram revealed a dense, circumscribed infiltration in the lingula which on laminagraphic studies did not appear to communicate with the bronchus. Roentgenographic examinations of the gastrointestinal and urogenital tracts were noncontributory. An exploratory thoracotomy was done. The tumor proved to be a *metastatic carcinoma* with the site of origin in the pancreas.

Intrathoracic extrapulmonary tumors may erroneously be considered as intrapulmonary if evaluation is incomplete. In instances of this kind a diagnostic pneumothorax may add considerable information to the problem.

Case 31. A 34-year-old male was admitted because of an interscapular pain. Roentgenographic examination of the chest revealed a large oval mass on the right at the level of the hilus. Laminagraphic studies and lateral view suggested the neoplastic nature of the mass which lay in the posterior gutter. A diagnostic pneumothorax was done. The tumor was found to be extrapulmonary. A diagnosis of *neurofibroma* was made which was confirmed at surgery.

In rare instances extrapulmonary intrathoracic neoplasms cannot be recognized as such even by supplementary methods such as diagnostic pneumothorax or bronchography. The writers had such an experience with a case of pleural mesenchymoma in which the tumor was located in the interlobar fissure and could not be distinguished from an intrapulmonary mass. Bronchography was misleading because the bronchi supplying the pulmonary segment in question

FIG. 32. Case 32. Mesenchymoma, located in the interlobar fissure.

appeared to be separated by the intervening mass. There was no evidence of compression or displacement of the lung with approximation of the bronchi, as would be anticipated with extrapulmonary tumors.

Case 32. A 51-year-old white male was admitted complaining of recent pain in the chest and symptoms of "influenza." He had been told six months prior to admission to the hospital that he had a "tumor of the right lung."

Roentgenographic examination of the chest showed a well-defined, oval shadow of homogeneous density in the right lung field, which in the lateral view appeared to lay within the interlobar fissure. The density of the mass was greater, however, than would be expected for an encapsulated effusion of equivalent size. Bronchography showed some separation of the bronchial branches, suggesting an intrapulmonary lesion. Bronchoscopy was negative. A thoracotomy was performed and a firm, nodular, slightly flat oval-shaped mass was removed from the pleura. The tumor was classified histopathologically as *pleural mesenchymoma.*

"Alveolar Cell" Carcinoma

Bronchogenic carcinoma of peripheral origin does not always follow the pattern of direct invasion of the bronchus with extension into the pulmonary parenchyma. A less frequent pattern is by extension within the respiratory passages and alveoli. This "alveolar cell carcinoma" (or "carcinomatous pneumonia") must be considered in lobar consolidations. Whether the exact site of origin is in the alveoli or in the smaller bronchioles has been a subject of considerable controversy. Herbut (4) has found by serial sections that these tumors originate from the mucosa of the minor bronchi and not from the cells lining the alveoli. He further observed that, if the malignant cells were squamous or undifferentiated, they usually filled the alveoli similar to inflammatory cells ("carcinomatous pneumonia"); if the cells were cuboidal or columnar, they formed an alveolar arrangement within the alveoli ("alveolar cell carcinoma"). These tumors extend within the pulmonary radicals, gradually filling the lung lobules with neoplastic cells until complete consolidation of a lobe has occurred. This is seen more frequently when the neoplastic cells are arranged in an organized alveolar fashion. In rare instances, the entire alveolar system may become filled with cells without parenchymal destruction. More frequently, only patchy areas of consolidation are found. This may be due to bronchogenic spread and implantation at distant sites. Furth (5) has been able to show bronchogenic dissemination of neoplastic cells (experimentally) to the alveoli where they rapidly proliferate and form a massive intra-alveolar growth of metastatic tumor cells.

The following case is an example of alveolar cell carcinoma with lobar consolidation as well as pulmonary dissemination. This medical history is somewhat unusual in that the patient lived two years following the generalized pulmonary dissemination of neoplastic cells as observed by roentgenographic studies.

Case 33. This 40-year-old white male had a chronic cough with blood-streaked sputum for nine months prior to his first admission. His general condition was good otherwise. Repeated sputum studies and gastric washings were negative for tubercle bacilli or fungi, but revealed the presence of malignant cells. Bronchoscopy was negative.

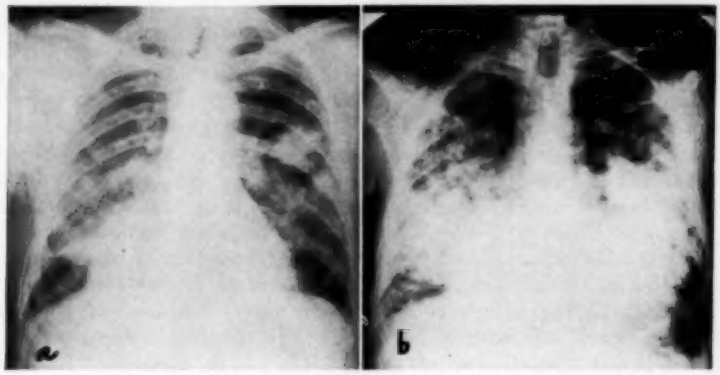
Roentgenographic examination of the chest showed a fairly large area of increased density in the inner zone of the right lung field and fairly numerous, somewhat irregular, nodular densities scattered throughout both lung fields. Little change was noted in the patient's course for approximately eight months. Subsequently, however, the cough became more severe; sustained fever and increasing hemoptysis were noted. Repeated roentgenographic examinations of the chest showed a diffuse, confluent, large, nodular infiltration throughout both lungs with the exception of the apices. These findings were suggestive of diffuse carcinomatosis. The patient died twenty-three months after the initial admission. Post-mortem examination revealed *alveolar cell carcinoma*.

Pulmonary Adenomatosis

A disease closely allied to "alveolar cell carcinoma" is "pulmonary adenomatosis" which presents a benign histologic picture, yet a malignant clinical course. The disease has been fatal in all of the cases reported in man. Although until 1945 only 10 cases had been reported, it is probable that the incidence may be higher than this figure would indicate. The etiology of this disease is uncertain,

and the pathogenesis is not well understood. The histopathologic changes are indistinguishable from those seen in a progressive pneumonia (verminous pneumonia or Jaagsiekte) of sheep, which is caused by a virus. Whether or not the counterpart in man has a similar etiologic background is highly questionable. There is no known communicability between sheep and man. Afebrile, progressive dyspnea with a marked increase in pulmonary secretions is the typical clinical picture.

The disease is characterized histologically by marked proliferation of tall, nonciliated, columnar epithelium within the alveoli which apparently spreads from the point of origin to involve more and more of the pulmonary aerating



Case 33

FIG. 33. (a). Admission roentgenogram, showing lobar consolidation on the right with a disseminated infiltration process throughout both lung fields. The sputum contained malignant tumor cells.

(b). Twenty-three months after admission. The disease has progressed. Except for the absence of cavitation, the appearance is not unlike tuberculosis or fungus disease of the lungs.

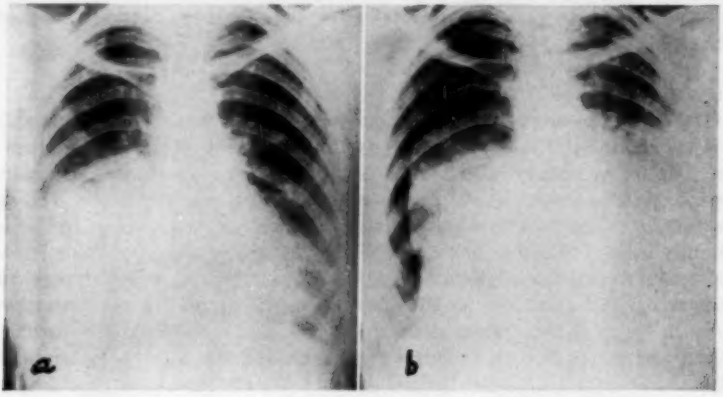
system. The alveolar walls become lined with this tall, columnar epithelium which soon becomes papillary, forming a cystadenomatous histologic picture. There is no invasion of the stroma, and the absence of mitotic figures is conspicuous. Metastases rarely occur. The origin of the proliferating epithelium seems to be from the alveolar wall or respiratory bronchioles. The writers believe that this disease merely represents a form of bronchogenic carcinoma which displays benign histopathologic manifestations.

Case 34. A 32-year-old white female had an unproductive cough for five months which eventually became productive of small amounts of mucopurulent sputum. She had low-grade fever from time to time, and lost ten pounds in weight. Malaise was marked. Physical examination on admission to the hospital revealed flatness and rales over the base of the right lung and a temperature of 99.8°F. Repeated sputum studies for tubercle bacilli and other microorganisms were negative. The erythrocyte sedimentation rate was 30 mm. per

hour. The total leukocyte and erythrocyte counts were within normal limits. Bronchography and bronchoscopy revealed no abnormalities.

Roentgenographic examination revealed a flocculent ill-defined infiltration of the right lower lobe. No abnormalities of the bronchi were noted by bronchography and laminagraphy. A diagnostic pneumothorax showed that the process had not extended to the chest wall and was not accompanied by intrapleural fluid. Roentgenographic studies three months later revealed extension to the right upper lobe and to the left lower lobe. There was no change in the nature of the infiltration.

During hospitalization the patient continued to have low-grade fever, weakness, and progressive weight loss. Dyspnea was marked and progressive, and she died three months after admission. Post-mortem examination showed that both lower lobes and the bases of the upper lobes and right middle lobe were firm and nodular. Only the apices were free of



Case 34

FIG. 34. (a). An ill-defined density is present in the right lower lobe. Bronchogram was negative. Laminagraphy likewise revealed no abnormalities of the bronchi.
(b). Diagnostic pneumothorax. The pleura separates readily thus indicating that the disease is restricted to the parenchyma.

disease. The microscopic picture was typical of pulmonary adenomatosis. There was no evidence of metastases anywhere in the body.

Pleural Effusion as a Manifestation of Bronchogenic Carcinoma

Pleural effusion is present in a significant number of cases of bronchogenic carcinoma. It is more frequently seen with the peripheral type of carcinoma which has involved the pleura by extension of the neoplastic process through the regional lymphatics into the superficial, subpleural lymphatic system. In approximately one-half of these cases the effusion is hemorrhagic and tends to reform rapidly after thoracentesis (6). Tumor cells may be found in the aspirated fluid, and the diagnosis of neoplasm may be thus confirmed. In some instances, the pleural effusion may be of non-neoplastic origin. Westermark (7, 8, 9) called attention to pleural effusion as a complication of the obstructive atelectasis which may be produced by carcinoma. If an obstruction persists over a long

period of time, inflammatory changes arise in the adjoining pleura. Moreover, empyema due to persistent secondary infection distal to the obstruction may result. The effusion may be bilateral and confined not only to the hemithorax of the primary malignancy.

The roentgenographic diagnostic difficulties encountered in the presence of large pleural effusions are chiefly a result of inadequate penetration of the pulmonary lesions and the lack of sharp delineation of such lesions against uninvolved portions of the lung. The writers have been able, in some instances, to demonstrate a primary tumor of the lung by body-section roentgenography after thoracentesis and introduction of pneumothorax. The ability to demonstrate such tumors depends to some extent on the "core density" of the tumor which is somewhat greater than that caused by atelectasis or hydropneumothorax alone.

Secondary Involvement of the Mediastinum

The clinical picture of bronchogenic carcinoma is, in some instances, modified and even entirely dominated by signs of mediastinal involvement. Paralysis of the diaphragm usually indicates the absence of a functioning phrenic nerve. Dysphagia due to esophageal involvement is not at all uncommon. The syndrome of superior vena caval obstruction is particularly interesting. The writers recently have observed 6 such cases. When this syndrome is found as a late development in patients in whom a primary pulmonary malignancy had previously been recognized, the cause for the obstruction is apparent. There are, however, cases in which the manifestations of this vascular involvement represent the initial and sometimes only clinical symptoms. Roentgenographic examination of the chest may or may not disclose evidence of an intrathoracic neoplasm, and so the bronchogenic origin of these malignancies may be completely overlooked. Two of the cases of superior vena caval obstruction in the present series warrant detailed presentation.

Case 35. A 49-year-old white male was admitted to the hospital complaining of nonproductive cough, progressive dyspnea, and orthopnea of three months' duration. Physical examination showed prominent neck veins and only slightly less prominent veins on the anterior chest wall. The lungs, heart, and abdominal organs appeared normal. The venous pressure in the right arm was 440 mm. of water and in the left arm 220 mm. The venous pressure in both legs was equal and measured 50 mm. of water. The circulation time from arm to tongue was 15 seconds.

Roentgenographic examination of the chest showed some cardiac enlargement and elevation of the right diaphragm, which moved on respiration. The lung fields were clear and the mediastinum was not widened. Venograms of both upper extremities showed obstruction at the junction of the subclavian and innominate veins bilaterally. There was a moderately developed collateral circulation emptying into the azygos system.

Bronchoscopy was attempted on three occasions, but had to be abandoned because of severe dyspnea. Laminagraphy was not helpful. The patient's general condition deteriorated rapidly as the signs of venous obstruction increased. He died three months after admission following an acute pulmonary hemorrhage.

Post-mortem examination revealed adenocarcinoma of the left main bronchus just below the carina. There was a small perforation of the left pulmonary artery due to erosion by the tumor. This was responsible for the terminal hemorrhage. The superior vena cava was incorporated in the tumor mass and was completely occluded by neoplastic growth.

The roentgenographic findings in this patient indicated obstruction of the veins entering the superior vena caval system without any definite signs of respiratory obstruction. This was well in keeping with the syndrome of a mediastinal tumor. Nevertheless, the mediastinum showed no deviation from normal; hence, provided no objective evidence of primary disease. The moderate cardiac enlargement suggested the possibility of a primary cardiac tumor. Celothelioma of the pericardium, which has been described as a cause of the superior vena caval syndrome by Hansson and Soderstrom (10), was considered as a possibility, but the patient did not have a coexistent symptom complex

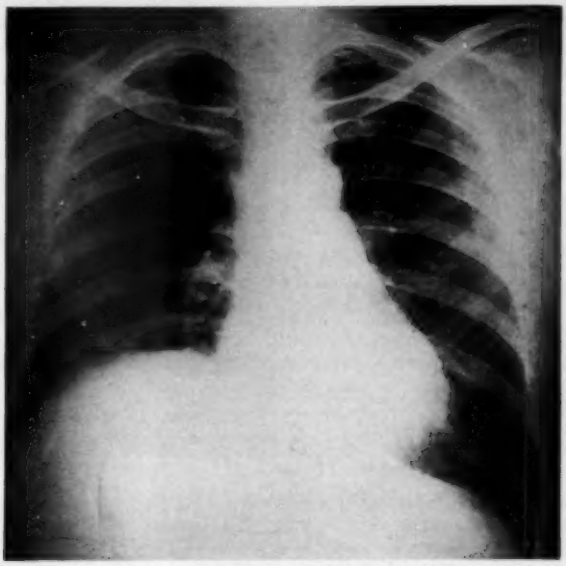


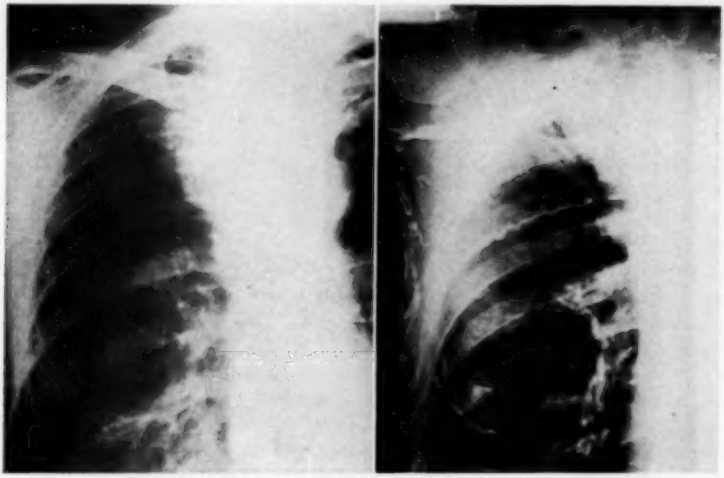
FIG. 35. Case 35. Absence of abnormal pulmonary shadows despite the presence of bronchogenic carcinoma arising in the left upper lobe bronchus. The superior vena cava is obstructed by a metastatic lesion in the mediastinum.

warranting such a conclusion. A constrictive pericarditis was excluded by the fact that there were no clinical signs of the disease, and because the obstruction was limited to the distribution of the superior vena cava. The best possibilities seemed to be either a thrombotic process occluding the lumen of the vena cava superior and its chief tributaries or a neoplastic process involving these areas. Spontaneous thrombosis seemed remote. Therefore, based on these deductions, a roentgenographic diagnosis was made of superior vena caval obstruction, probably due to invasion by bronchogenic tumor.

Case 36. A 69-year-old white male was admitted to the hospital because of increasing swelling of the neck for the past month, associated with exertional dyspnea and orthopnea. Physical examination revealed moderate dilatation of the veins of the neck and upper

thorax. The heart and lungs were normal. Venous pressure in both upper extremities was increased, measuring 390 mm. of water in the right arm and 300 mm. of water in the left. The pressure in both lower extremities was equal and measured 80 mm. of water.

Roentgenographic examination of the chest showed a mass with a scalloped border in the right lung field adjacent to the mediastinum. The mediastinal nodes were enlarged, and on fluoroscopy the diaphragm showed paradoxical motion. Fluoroscopy of the pharynx and esophagus showed displacement of the hypopharynx and upper segment of the esophagus to the left. A venogram of the right upper extremity showed an irregular narrowing of the distal segment of the subclavian and the innominate vein and a definite obstruction of the superior vena cava. The collateral circulation was well developed, and the venous return



Case 36

FIG. 36. (a). Dense mass in the inner zone of the apex of the left lung thought to be due to mediastinal widening.

(b). Venogram showing obstruction of the superior vena cava. The collateral circulation emptying into the azygos is well demonstrated. This localizes the lesion in the superior cava above the entrance of the azygos and below the bifurcation.

from the upper extremity was chiefly through intercostal veins emptying into the azygos. The obstruction was thus localized to the superior vena cava above the entrance of the azygos vein. In view of these roentgenographic findings, a diagnosis of bronchogenic carcinoma with neoplastic involvement of the vena cava superior was suggested. Bronchoscopy revealed no abnormalities. Nevertheless, post-mortem examination subsequently revealed primary carcinoma of the right upper lobe bronchus with metastases to the mediastinum and obstruction of the superior vena cava above the azygos.

The syndrome of superior vena caval obstruction is not a frequent feature of bronchogenic carcinoma, nor is it limited to diseases originating in the thoracic cavity. It is significant, however, that approximately 50 per cent of the cases of this syndrome are apparently due to thoracic tumors of primary or metastatic origin. Thirty-five per cent of the cases are estimated to be due to aortic aneurysm

and the remaining 15 per cent are due to a variety of rare causes, some undetermined. The obstruction of the superior vena cava in cases of bronchogenic carcinoma, and most likely in other tumors, is usually due to metastatic involvement of mediastinal nodes and extension of the tumor within the mediastinum leading to compression of the vein and sometimes to invasion of the lumen where large neoplastic thrombi may be formed.

Limitations of Diagnostic Procedures

Certain of the limitations of the roentgenographic diagnosis of bronchogenic carcinoma have been presented. In spite of these limitations, roentgenography is obviously the most reliable method for the detection of pulmonary lesions to which serious consideration of malignancy must be given. The accuracy of the roentgenographic diagnosis is actually high in patients who manifest pulmonary lesions which present a somewhat typical clinical behavior, or in patients presenting symptoms which are directly referable to the respiratory tract. What roentgenographic evidence lacks are the signs which are in themselves so characteristic that they cannot be indicative of other diseases. It seemed proper to the writers to emphasize the nonspecific character of the roentgenographic manifestations of bronchial carcinoma when involvement is limited to pulmonary structures. It is clear that there are no signs indicative of an inflammatory disease which could not be, or are not, present in cases of bronchogenic carcinoma. Bronchogenic carcinoma does not really "simulate" other diseases, as is frequently stated, but causes roentgenographic pulmonary opacities which happen to have been caused by cancer rather than by other primary agents. Some changes observed in carcinoma are of secondary nature and do not differ pathologically from their non-neoplastic counterparts. Once these facts are considered, further investigation is implemented by additional methods which form an important chain in the clinical studies. These include bronchoscopy, sputum examinations, and other clinical and laboratory observations.

To stress the need for bronchoscopy is superfluous, for it constitutes an integral part of the diagnostic armamentarium in chest diseases. Its role is twofold: it aids in the demonstration of intrabronchial lesions which might not otherwise be recognized histologically; and it may indirectly determine the operability of a demonstrated tumor. The writers believe, however, that the frequency with which bronchoscopy establishes the early diagnosis of bronchial carcinoma has been overestimated. Certainly the procedure is of little, if any, value in establishing the diagnosis of the peripheral type of carcinoma, since this area is not accessible to the bronchoscope. Moreover, bronchoscopy is frequently of very little value when the upper lobe bronchi are involved. Graham (11) and Rubin (12) believe that a positive diagnosis of carcinoma of the lung can be made in 70 to 80 per cent of cases by this procedure. However, Arkin and Wagner (13) found bronchoscopy necessary to make the diagnosis in only 10 per cent of 135 cases studied. In the writers' experience, bronchogenic tumors were only rarely demonstrated in the absence of roentgenographic evidence of disease, and bronchoscopy was more helpful in confirming the diagnosis than in demonstrating an otherwise

undiagnosed lesion. Indirect bronchoscopic evidence of pulmonary tumor is of no greater value than the evidence obtained from clinical and roentgenographic examinations. The diagnosis of carcinoma by bronchoscopy can be considered to be an accurate procedure only when the findings are confirmed by examination of removed tumor tissue.

Aspiration biopsy has been enthusiastically advocated by some (14) in the diagnosis of peripheral-type carcinoma. The procedure is hazardous, however, because of the danger of complications such as infection, bronchopleural fistula, and dissemination of tumor cells to the pleura and duct wall. The procedure should certainly not be attempted without the aid of the biplane fluoroscope.

Sputum examination for neoplastic cells has become of increasing value (15); but here, too, there are definitely limiting factors. The diagnosis of neoplastic cells alone is not adequate unless the site of the lesion can be localized. It would obviously be difficult to undertake a thoracotomy on the basis of demonstrated tumor cells alone. It may even be questioned whether such a demonstration is possible in the early stage of the disease. Only a careful investigation based on close cooperation between the clinician, bronchoscopist, radiologist, and pathologist can increase the accuracy of early diagnosis when the presence of the disease is even remotely suspected.

SUMMARY

Bronchogenic carcinoma which arises from the peripheral bronchi and bronchioles produces relatively few clinical symptoms before metastatic lesions are manifest. This results from the absence of obstruction of large bronchi. Roentgenographic and other collateral studies are often inconclusive, so that it frequently becomes necessary to resort to diagnostic thoracotomy.

The roentgenographic manifestations of circulatory and inflammatory infiltrations may be similar to the circumscribed peripheral tumors. In these cases, collateral laboratory and clinical manifestations may add enough additional information to permit a diagnostic conclusion. Laminagraphic studies are of value in such situations, and cardioangiography is of particular value in differentiating circulatory from neoplastic lesions.

By the use of a diagnostic pneumothorax, intrathoracic extrapulmonary lesions may usually be differentiated from the intrapulmonary ones.

The roentgenographic manifestations of alveolar cell carcinoma may closely resemble inflammatory infiltrations. "Pulmonary adenomatosis" is probably a variant of this type of peripheral bronchogenic carcinoma.

It is believed that metastatic lesions occur virtually simultaneously with the origin of primary bronchogenic carcinomas of any cellular type. Therefore, by present-day clinical and laboratory procedures including bronchoscopy, a diagnosis of "early" carcinoma can be made in only a small percentage of cases even under optimum circumstances. Hence it is only by maintaining close cooperation between the clinician, radiologist, bronchoscopist, pathologist, and surgeon that our diagnostic efficiency can be increased so that it is of any value whatsoever to the patient.

SUMARIO

El Carcinoma Broncógeno como Problema de Diagnóstico Diferencial en las Afecciones Pulmonares: III. Forma Periférica; Carcinoma Originado en los Bronquios Menores y Bronquiolos

El carcinoma broncógeno que tiene su origen en los bronquios y bronquiolos periféricos produce relativamente pocos síntomas clínicos antes de aparecer lesiones metastáticas, lo cual se debe a la falta de oclusión de los bronquios grandes. Los estudios roentgenológicos y otros colaterales resultan a menudo ambiguos de modo que frecuentemente se vuelve necesario recurrir a la toracotomía diagnóstica.

Las manifestaciones radiológicas de las infiltraciones circulatorias e inflamatorias pueden ser bastante semejantes a las de los tumores periféricos circunscritos. En esos casos, los hallazgos colaterales obtenidos en el laboratorio y en la clínica pueden aportar suficiente información adicional para permitir una conclusión diagnóstica, y los estudios laminagráficos también resultan de valor. La cardioangiografía es del mayor valor para diferenciar las lesiones circulatorias.

Mediante el empleo de un neumotórax diagnóstico, pueden habitualmente diferenciarse las lesiones extrapulmonares intratorácicas, de las intrapulmonares.

Las manifestaciones roentgenológicas del carcinoma de las células alveolares pueden ser muy semejantes a las de las infiltraciones inflamatorias. La "adenomatosis pulmonar" es probablemente una variante de esa forma de carcinoma broncógeno periférico.

Opinan las AA. que ocurren lesiones metastáticas casi simultáneamente con la iniciación de carcinomas broncógenos primarios de cualquier forma celular, por lo cual, con los actuales procedimientos clínicos y de laboratorio, no cabe hacer el diagnóstico de carcinoma "incipiente" más que en un pequeño porcentaje de los casos, aun en las circunstancias más favorables. El examen broncoscópico tiene sus limitaciones bien definidas. Sólo mediante la íntima cooperación entre el clínico, el radiólogo, el patólogo y el cirujano puede acrecentarse nuestra eficacia diagnóstica de modo que posea algún valor real para el enfermo.

RESUME

Cancer bronchiogénique considéré comme un problème de diagnostic différentiel dans les affections du poumon: III. Type périphérique; épithélioma primitif des petites bronches et des bronchioles

Le cancer bronchiogénique qui débute dans les bronches périphériques et les bronchioles détermine relativement peu de signes cliniques avant la production de métastases. Ceci est explicable en raison de l'absence d'obstruction au niveau des grosses bronches. Les études radiologiques et autres études parallèles sont souvent peu concluantes, il est donc souvent nécessaire de faire appel à la thoracotomie pour le diagnostic.

L'image radiologique de l'infiltration des tissus d'origine circulatoire et inflammatoire peut être la même que celle des tumeurs circonscrites de la périphérie. Dans ces cas, les examens de laboratoires et les manifestations cliniques peuvent apporter des indications supplémentaires qui permettent d'établir un diagnostic. L'étude tomographique est également très utile. L'angio-cardiogra-

phie est d'une valeur particulière pour la différenciation des lésions de l'appareil circulatoire.

L'usage du pneumothorax pour le diagnostic des lésions extra-pulmonaires intrathoraciques permet habituellement de les distinguer des lésions intrapulmonaires.

Les signes radiologiques de l'épithélioma alvéolaire sont très voisins de ceux produits par les réactions inflammatoires. "L'adénomatose pulmonaire" est probablement une variante de cette forme de cancer bronchiogénique périphérique.

Les auteurs considèrent que les lésions métastatiques se produisent pratiquement en même temps que se constitue le cancer bronchiogénique primitif, quelque soit le type cellulaire auquel il appartient. En conséquence, dans l'état actuel des procédés cliniques ou des techniques de laboratoire dont nous disposons, le diagnostic de cancer "au début" ne peut être fait que dans un faible pourcentage des cas, même dans les conditions les plus favorables. L'examen bronchoscopique a des limites déterminées. Ce n'est que par une coopération étroite entre le clinicien, le radiologue, l'anatomo-pathologiste et le chirurgien que sera réalisée l'efficacité du diagnostic, en ce qui concerne son utilité pour le patient.

REFERENCES

(1) Fried, B. M.: Bronchogenic carcinoma: A study of 152 autopsied cases, Acta Union Internat. contre Cancer, 1938, *3*, 153.

(2) Tuttle, W. C., and Womack, N. A.: Bronchogenic carcinoma: A classification in relation to its treatment and prognosis, J. Thoracic Surg., 1934, *4*, 125.

(3) Adams, R.: Primary lung tumors, J.A.M.A., 1946, *130*, 547.

(4) Herbut, P. A.: Bronchiolar origin of "alveolar cell tumor" of the lung, Am. J. Path., 1944, *20*, 911.

(5) Furth, J.: Experiments on the spread of neoplastic cells through the respiratory passages, Am. J. Path, 1946, *22*, 1101.

(6) Olin, H. A., and Elliot, C. A.: Primary bronchogenic carcinoma of the lung, Am. J. Surg., 1941, *54*, 614.

(7) Westermark, N.: On bronchostenosis: A roentgenological study, Acta radiol., 1938, *19*, 285.

(8) Westermark, N.: On the roentgen diagnosis of primary tumors of the lung, Acta radiol., 1938, *19*, 505.

(9) Westermark, N.: Bronchial carcinoma of the lung, Am. J. Roentgenol., 1939, *41*, 493.

(10) Hansson, C. J., and Soderstrom, N.: Celothelioma of the pericardium, Acta radiol., 1943, *24*, 183.

(11) Graham, E. A.: Primary carcinoma of the lung or bronchus, Ann. Surg., 1936, *103*, 1.

(12) Rubin, E. H.: Diseases of the Chest, W. B. Saunders, Philadelphia, 1947.

(13) Arkin, A., and Wagner, D.: Primary carcinoma of the lung: A diagnostic study of 135 cases, J.A.M.A., 1936, *106*, 587.

(14) Craver, L. F.: Diagnosis of malignant lung tumors by aspiration biopsy and sputum examination, Surgery, 1940, *8*, 947.

(15) Herbut, P. A., and Clerf, L. H.: Bronchogenic carcinoma, J.A.M.A., 1946, *130*, 1006.

(16) Moyer, J. H., and Ackerman, A. J.: Bronchogenic carcinoma as a differential diagnostic problem in pulmonary disease: I. Carcinoma arising from major bronchi uncomplicated by secondary infection, Am. Rev. Tuberc., 1951, *63*, 176.

(17) Moyer, J. H., and Ackerman, A. J.: Bronchogenic carcinoma as a differential diagnostic problem in pulmonary disease: II. Carcinoma arising from major bronchi complicated by secondary infection, Am. Rev. Tuberc., 1951, *63*, 255.

BENIGN SPONTANEOUS HEMOPNEUMOTHORAX[1]

LEROY HYDE AND BERNARD HYDE

(Received for publication August 31, 1950)

INTRODUCTION

Examination of the medical literature (1–4) yields the impressions that spontaneous hemopneumothorax is very rare and that spontaneous hemopneumothorax is usually fatal. It is believed that neither of these statements is true.

The medical literature contains reports of approximately 60 cases of spontaneous hemopneumothorax with the autopsy findings in 14 patients who died. There is a natural tendency to report cases with autopsy findings rather than patients who have recovered and remained well. The present report concerns 12 patients with benign idiopathic spontaneous hemopneumothorax, each of whom had a relatively uncomplicated course with full recovery and no complications. It is believed that spontaneous hemopneumothorax is but a variation of the more commonly described benign spontaneous pneumothorax (5). The former has the added complication of a tear of a pleural adhesion or an emphysematous bleb with gross bleeding into the pleural cavity.

INCIDENCE

Benign idiopathic spontaneous hemopneumothorax is neither a common nor a rare condition and presumably there have been many more cases than the 60 reported in the literature. Recently, Rottenberg and Golden (6) noted 3 patients with spontaneous hemopneumothorax in a series of 97 patients with spontaneous pneumothorax, and Hansen (7) reported another 3 cases, including one in a female patient. Solovay (8) added another case report. In the writers' series of 112 consecutive cases of benign idiopathic spontaneous pneumothorax, there were 5 patients who had grossly bloody pleural fluid (spontaneous hemopneumothorax), an incidence of 4 per cent. Of those cases reported in the literature, all patients but 2 have been men and the 12 patients of the present study were all men. The age incidence reported in the literature has been quite constant, with most of the cases occurring between twenty and forty years of age. The 12 patients of the present report ranged in age from twenty to forty-four years.

PATHOGENESIS

The pathogenesis of spontaneous pneumothorax or spontaneous hemopneumothorax has not yet been established. Exertion or trauma are usually not causal factors. Various theories have been presented including rupture of a valvelike vesicle situated on or near the pleural surface; congenital pleural defect with the formation of pleural blebs; rupture of a thin mediastinal pleura, permitting air to escape into the pleural cavity; and rupture of a pleural bulla secondary to

[1] From the Long Beach VA Hospital, Long Beach, California, and the College of Medical Evangelists, Los Angeles, California.

localized interstitial subpleural emphysema. In several of the autopsies in fatal cases of spontaneous hemopneumothorax, torn adhesions and ruptured bullae as well as adhesions may be richly vascularized. Nevertheless, the source of bleeding cannot always be ascertained at autopsy.

Hemopneumothorax may occur in tuberculosis, but in such instances the tuberculous disease is usually both obvious and advanced (9). Consequently, cases in which tuberculosis is not obvious or easily discovered at the time of the spontaneous hemopneumothorax may be considered to be probably nontuberculous. Hemopneumothorax is uncommon even in advanced pulmonary tuberculosis. Neoplastic disease with involvement of the pleura occasionally gives rise to hemopneumothorax (3).

CLINICAL MANIFESTATIONS

The clinical picture of hemopneumothorax is very similar to that of benign idiopathic spontaneous pneumothorax, which has been previously described (5). There are, however, two additional complications: the greater likelihood of shock, and the rapid development of anemia due to extensive bleeding into the pleural cavity. The usual history is that of a young adult male, between twenty and forty years of age, who is between fifteen and forty-five pounds underweight, and who, while at rest or at mild activity, suffers a sharp, sudden, unilateral severe pain of the anterior chest. The physical examination reveals the previously healthy patient to be dyspneic, probably cyanotic, splinting one side of his chest, and in a state of semi-shock or actual shock. The affected side of the chest is flat to percussion with absent breath sounds, and thoracentesis yields grossly bloody fluid. It is believed by some that cardiac and respiratory movements defibrinate the blood in the pleural cavity, producing fibrin deposits on the pleura and leaving most of the blood unclotted. Blood in the pleural cavity may contain no fibrinogen, prothrombin, or thrombin.

The chest roentgenogram reveals a hydropneumothorax. The fluid level is usually between the fourth and eleventh ribs posteriorly. The leukocyte count is usually within normal limits although the erythrocyte sedimentation rate may be slightly elevated or normal.

TREATMENT

Therapy is directed toward the general condition of the patient (management of shock, transfusions, and similar procedures) and his thoracic ailment (thoracentesis of bloody fluid and, perhaps, withdrawals of intrapleural air if there is any dyspnea). Decortication may be necessary later to remove the dense, gelatinous, hemorrhagic layer adjacent to the pleura. The optimum time for this procedure, if indicated, is usually four to eight weeks after the intrapleural bleeding. Only one of the patients in the present study required decortication. It should be mentioned that encouraging results have been observed from the early use of preparations of the enzyme streptokinase-streptodornase in cases of hemothorax (10, 11).

RECURRENCE

No patient of the present series had a recurrent spontaneous hemopneumothorax. One patient (Case 9) had two spontaneous pneumothoraces, but these were on the opposite side (right) to the original spontaneous hemopneumothorax (left). Pleural adhesions and fibrosis secondary to the bloody fluid apparently prevent recurrence on the same side.

Observations for periods varying from one to eight years are available for the 12 patients. In no instance was pulmonary tuberculosis present and all 12 patients are in good health at present.

CASE REPORTS

Case 1. J. H. was a 44-year-old white male. He was awakened by sudden left anterior chest pain while lying in bed. A chest roentgenogram revealed fluid up to the level of the ninth posterior rib with air above that level. No pleural adhesions were present. There was moderate dyspnea but no cyanosis. The left lung was between 90 and 95 per cent collapsed. A single thoracentesis yielded grossly bloody fluid. The patient required eighty days for the disappearance of the intrapleural blood and expansion of the left lung. There has been no recurrence. The hemoglobin was 14.5 gm. per 100 cc. and the total leukocyte count was 10,300 per cu. mm. The patient had a low-grade fever for one month but this was due to a complicating thrombophlebitis of both legs.

A six-year follow-up of this patient reveals him to be well and without recurrence. There was no evidence of tuberculosis.

Case 2. J. M. was a 31-year-old white male who developed sudden left anterior chest pain with slight dyspnea but no cyanosis. The chest roentgenogram revealed 15 per cent collapse of the left lung with fluid up to the level of the ninth posterior rib. Thoracenteses yielded grossly bloody fluid. The hemoglobin was 14.2 gm. per 100 cc. and the total leukocyte count was 5,800 per cu. mm. This patient required fifty days to re-expand his left lung. His course was complicated by low-grade fever following a two-week period of normal temperature. This second bout of fever was caused by thrombophlebitis of the left leg.

The patient was followed for eight years and has remained well without any recurrence of his spontaneous hemopneumothorax or the development of any other pulmonary disease.

Case 3 A.. H., a 36-year-old white male, while at rest had a sudden, sharp, left anterior chest pain which was very severe and aggravated by breathing. He was thirty pounds underweight. Examination revealed decreased fremitus over the left chest with hyper-resonance over the upper lung field and dullness to flatness over the lower half of the left lung. Breath sounds were diminished to absent throughout the entire left chest. The systolic blood pressure was 134 mm. of mercury and the diastolic pressure 96 mm. The erythrocyte count was 4.8 million cells per cubic millimeter; the total leukocyte count was 5,800; and the hemoglobin was 15 gm. per 100 cc. The differential leukocyte count was normal except for 5 per cent eosinophils. The erythrocyte sedimentation rate was 19 mm. in the first hour (Wintrobe). A serologic test for syphilis (Kahn) and urine examinations were negative. Thoracentesis two days after the acute episode yielded 800 cc. of grossly bloody fluid. Examination of the blood removed from the left pleural cavity was negative for tumor cells, pyogens, and tubercle bacilli on concentrate and culture. Three gastric lavages were negative for tubercle bacilli on concentrate and culture. The chest roentgenogram revealed fluid up to the level of the seventh rib posteriorly. The right lung was clear. A chest film thirty days after the

onset revealed considerable re-expansion of the left lung with approximately 30 per cent collapse. Fluid was present to the level of the eleventh posterior rib, and the heart was in the midline. The patient was afebrile and asymptomatic throughout. The highest temperature was 99° F. The left lung was fully expanded on the forty-first day following the onset of the severe left chest pain. Some pleural reaction could still be seen. The patient had no further pulmonary difficulty and returned to work.

Follow-up examination one year later revealed that this patient had no pulmonary disease and a chest roentgenogram at that time was entirely normal.

Case 4. D. K. E., a 27-year-old white male, was admitted to the hospital with sudden, severe, right chest pain of three days' duration. There was some slight dyspnea but no cough, sputum, hemoptysis, fever, or previous weight loss. There was no history of tuberculosis. The physical examination revealed a thin (approximately thirty pounds underweight) man in no acute distress. There was evidence of a right hydropneumothorax. The erythrocyte count was 3.6 million cells per cu. mm.; the hemoglobin, 11.25 gm. per 100 cc.; the total leukocyte count was 15,000 per cu. mm. with a normal differential. The erythrocyte sedimentation rate was 48 mm. in the first hour. A serologic test for syphilis (Wassermann) and urinalysis were negative. Five sputum specimens were negative for tubercle bacilli on concentrate and culture. Tuberculin, coccidioidin, and brucellin skin reactions were negative. The chest roentgenogram revealed a right hydropneumothorax with a fluid level reaching to the ninth posterior rib. The left lung was clear. Repeated thoracenteses yielded grossly bloody fluid with no evidence of malignant cells, pyogens, or tubercle bacilli on concentrate and culture. The patient was treated with bed rest and remained afebrile throughout. His chest pain disappeared shortly after admission. With an adequate diet and iron medication, the erythrocyte count rose to 4.56 million per cu. mm. and hemoglobin to 14.0 gm. per 100 cc. The erythrocyte sedimentation rate remained elevated, 48 and 51 mm. in the first hour (Wintrobe method). A chest film twenty days after the onset revealed practically complete re-expansion of the right lung with a minimal amount of fluid still present.

The patient left the hospital on a pass and did not return, so that follow-up is not available. At the time of leaving, however, he was quite well and probably would have required only an additional week for complete re-expansion and disappearance of the small amount of residual fluid. The last erythrocyte sedimentation rates obtained were 14 and 25 mm. in one hour. The time for re-expansion of the right lung and absorption of the bloody fluid in the right pleural cavity was approximately thirty days. There was no evidence of tuberculosis.

Case 5. W. G. S. was a 38-year-old white male. His past history revealed a right spontaneous hemopneumothorax six weeks previous to the present admission. He had had two thoracenteses, yielding grossly bloody fluid of unknown amounts, and had been hospitalized for eleven days. It is not known whether his right lung was completely re-expanded at discharge from the hospital or whether the blood in the right pleural space was totally absorbed. When first seen by the writers, the pneumothorax space was not present but fluid was seen in the right pleural space to about the level of the eleventh posterior rib. The past history was significant only in that one brother had died of tuberculosis six years previously.

Physical examination revealed a thin man (twenty pounds underweight) who did not appear acutely ill. The positive physical findings were delayed excursion of the right chest, decreased tactile fremitus, and impaired resonance to percussion over the lower half of the right lung anteriorly and posteriorly. The breath sounds were decreased in this area and occasional expiratory wheezes were noted. The patient was afebrile and asymptomatic throughout hospitalization, the highest temperature being 99.2° F. Thoracentesis on the right yielded 200 cc. of grossly bloody fluid, which was negative for pyogens and tuber-

cle bacilli on concentrate and culture. Numerous gastric washings were also negative for tubercle bacilli on concentrate and culture. Coccidioidin skin reaction was negative; and a positive reaction to tuberculin PPD No. 1 was observed. The roentgenogram became entirely normal seventy-five days after the onset. Erythrocyte counts were normal. The total leukocyte count was 9,800 cells per cu. mm. and the erythrocyte sedimentation rate was 2 mm. in one hour.

The patient has been well for one year and three months following discharge.

Case 6. W. L. S., a 30-year-old white male, developed a sudden, severe, left chest pain with substernal pressure, dyspnea, and faintness. He was hospitalized immediately. The temperature on admission, and the highest temperature, was 99.6° F., which persisted for three days and was thereafter normal. The chest film on admission revealed a left hydropneumothorax with approximately 80 per cent collapse of the left lung and a marked shift of the mediastinum to the right. Physical examination revealed hyper-resonance over the upper one-third of the left lung, with dullness to flatness and absent breath sounds over the lower two-thirds of the left lung. Left thoracentesis yielded 1,500 cc. of air and 125 cc. of grossly bloody fluid. The aspirated fluid was negative for pyogens and tubercle bacilli on concentrate and culture. On admission, the erythrocyte count was 4.79 million per cu. mm., the total leukocyte count was 19,500 per cu. mm., and the hemoglobin was 14.75 gm. per 100 cc., with a normal differential. The erythrocyte sedimentation rate was 5 mm. in the first hour. Subsequent blood counts were within normal limits, except for a 5 per cent eosinophilia on one occasion. The coccidioidin skin reaction was negative; the tuberculin PPD No. 1 skin reaction was positive. Three gastric washings were negative for tubercle bacilli on concentrate and culture. The patient was treated with bed rest without any other therapy following the first thoracentesis. Serial chest films revealed gradual expansion of the left lung and absorption of the blood in the left pleural cavity. The last chest film taken thirty-eight days following the onset disclosed a completely re-expanded left lung. The patient convalesced at home for one week and then returned to work and has been well ever since.

Follow-up thirteen months later revealed the patient to be in perfectly good health and his chest roentgenogram was normal. There was no evidence of tuberculosis.

Case 7. R. K., a 21-year-old white male electrician, was admitted to the hospital with a ten-day history of dyspnea, right lower chest pain, anorexia, and a cough productive of approximately 15 cc. of greenish-yellow sputum which had been bright red in color one day approximately a week prior to admission. Dyspnea had been present for five days prior to admission. The physical examination revealed a dyspneic, well-developed, well-nourished man. The positive findings included impaired respiratory excursion of the right thorax, flatness to percussion of the lower half of the right chest anteriorly and posteriorly, with diminished tactile fremitus and vocal fremitus and absent breath sounds in this area. No rales were heard. The blood pressure was 110 systolic and 74 diastolic in mm. of mercury. The chest roentgenogram revealed a massive right hydropneumothorax. The temperature on admission was 100.4° F. This returned to normal in six days and remained so. The erythrocyte count was 4.3 million per cu. mm., the total leukocyte count was 6,700 per cu. mm. with 80 per cent polymorphonuclear leukocytes, and the erythrocyte sedimentation rate was 25 mm. in one hour. A serologic test for syphilis (Kahn) and urinalysis were negative. Thoracentesis was done, and 550 cc. of dark, grossly bloody fluid were removed from the right chest. This was repeated several times. Studies of this fluid and of the sputum were negative for both acid-fast bacilli and tumor cells. Coccidioidin, histoplasmin, and tuberculin PPD No. 1 and No. 2 skin reactions were negative. The right lung re-expanded and the pleural reaction had almost completely disappeared, as shown on the roentgenograms,

twenty-three days after the onset. There was some residual minimal blunting of the right costophrenic angle.

The patient was well one year later.

Case 8. J. J. D., a 23-year-old white male, was awakened by a severe, knifelike pain in the right upper chest anteriorly and severe dyspnea. The past history was noncontributory except for several bouts of pneumonia two or more years previously. The physical examination revealed a fairly well nourished, acutely ill man. There was diminished expansion of the right chest with flatness and absent breath sounds below the level of the third rib anteriorly on the right. The blood pressure was 110 systolic and 80 diastolic in mm. of mercury; and the pulse rate, 120 per minute. On admission, the erythrocyte count was 2.3 million cells per cu. mm. with a hemoglobin of 65 per cent. The total leukocyte count was 3,600 per cu. mm. with 75 per cent neutrophils. The chest roentgenogram revealed a right hemopneumothorax with a slight shift of the heart and mediastinum to the left. Several right thoracenteses were done with the removal of 500 to 800 cc. of grossly bloody fluid each time. Because of the patient's anemia, he was given plasma and blood transfusions. Grossly bloody fluid continued to reaccumulate in the right pleural cavity with the fluid level usually being above the clavicle anteriorly. This continued for a three-month period, at which time a right decortication was done because of a fibrinous membrane around the right lung. The patient did well, with the right lung re-expanding completely.

Follow-up examinations two years after discharge were entirely negative except for a history of a bout of right lower lobe pneumoccocal pneumonia which had been treated with penicillin with prompt recovery.

Case 9. D. S., a 20-year-old Japanese male, was seen October 11, 1939 because of sharp, left anterior chest pain, worse on respiration, and dyspnea. A left spontaneous pneumothorax was found. The left lung gradually expanded with bed rest, but two weeks later, on October 25, the patient had further left chest pain, and the left lung was found to be collapsed, with a large amount of fluid present. Thoracentesis revealed grossly bloody fluids. A small, right spontaneous pneumothorax was noted at the same time. With bed rest and three left thoracenteses, both lungs were seen to be completely expanded on a roentgenogram obtained December 13. Six weeks later the patient had another right spontaneous pneumothorax which completely re-expanded within a period of three weeks on bed rest alone.

The patient has remained well save for recurrent, benign, idiopathic spontaneous pneumothorax on the right in November 1948 and again in October 1949. Re-expansion was uncomplicated each time.

Case 10. J. B.,[2] a 20-year-old male, had a sharp stabbing pain in the left anterior chest and went into shock on September 28, 1942. Examination of the chest revealed dullness and diminished breath sounds over the lower half of the left chest. The apex of the heart was pushed to the right. A benign idiopathic left spontaneous hemopneumothorax was found. The patient responded to twenty-five days of bed rest with two thoracenteses yielding grossly bloody fluid. He made an uneventful recovery with only slight residual left pleural thickening.

He was followed for three years, during which time he remained well. There was no evidence of tuberculosis at any time on serial chest roentgenograms.

[2] A patient of Dr. Charles Baron of Covington, Kentucky, who kindly furnished the details.

Case 11. J. G. C. was a 27-year-old white male who entered the hospital on August 13, 1949, with the history that two days previously, following some physical exertion, he developed sudden right severe chest pain, both anteriorly and posteriorly. This was associated with marked dyspnea which became progressively worse. There had never been a similar episode previously, and the past history was noncontributory. There was no family history of tuberculosis and no known exposure to tuberculosis. The physical examination on admission revealed an asthenic man who was underweight, extremely pale, and who appeared acutely ill. He had marked dyspnea and cyanosis. The systolic blood pressure was 135 mm. of mercury and the diastolic pressure 85 mm. The pulse rate was 92 per minute. The temperature was 98.6° F. Positive physical findings were limited to the chest, where it was noted that there was marked chest lag on the right. There was marked dullness to flatness to percussion over the right chest anteriorly and posteriorly, with absent breath sounds. The left lung was hyper-resonant to percussion. The right cardiac border could not be determined but the left border was in the anterior axillary line. The erythrocyte count on admission was 4.2 million cells per cu. mm. A chest roentgenogram revealed a right hydropneumothorax with a fluid level at the eighth posterior interspace. There was a right apical pleural adhesion. The mediastinum was shifted to the left, and the left lung was clear. Shortly after admission to the hospital, the patient's blood pressure dropped to 90 systolic and 40 diastolic in mm. of mercury, and his skin became cold and clammy. He was treated immediately with intravenous plasma, intranasal oxygen, and blood transfusions. The erythrocyte count had dropped to 3.8 million cells per cu. mm. He received daily right thoracenteses with the removal of grossly bloody fluid and some air and daily blood transfusions of 500 cc. to 1,000 cc. Serial chest roentgenograms revealed re-expansion of the right lung and gradual diminution of the bloody fluid in the right pleural space. The chest roentgenogram taken fifteen days after the onset revealed that most of the air and fluid had been removed from the right pleural space and that the right lung was practically completely expanded. No parenchymal infiltration was noted.

A follow-up chest film eleven months later revealed resorption of the right thickened pleura. Both lungs were clear.

Case 12. T. C. N., a patient with spontaneous hemopneumothorax, was seen on November 1, 1950. He revealed that he had had a spontaneous left pneumothorax two years previously. On the day prior to admission he had a severe right anterior chest pain radiating slightly upward to the neck, associated with dyspnea. The patient was standing still and there was no unusual effort involved. There were no chills, fever, cough, sputum, or blood-streaking. The family history is significant in that the father is being treated for pulmonary tuberculosis at the present time. Physical examination revealed a 21-year-old white male who did not appear acutely ill. The height was 6 feet, 2 inches; the weight, 148 pounds, indicating the patient was markedly underweight. The general physical examination was entirely normal. Examination of the chest revealed a lag over the right chest with hyper-resonance. No rales were heard and breath sounds were absent. The voice sounds "sounded like they came from a barrel." The admission erythrocyte count was 3 million cells per cu. mm., with hemoglobin of 10.5 gm. per 100 cc. The total leukocyte count was 7,500 cells per cu. mm. with a normal differential. A serologic test for syphilis (Kahn) was negative, and urine examinations were normal. A chest roentgenogram taken on admission revealed 20 per cent collapse of the right lung but no fluid. No parenchymal disease or infiltration could be seen. Chest roentgenogram taken three days later revealed complete collapse of the right lung and a large amount of fluid in the right pleural space. On this date, November 4, the temperature rose to 101° F. Right thoracentesis was performed and grossly bloody fluid aspirated. Fifteen hundred cubic centimeters of "pure blood" which did not clot were removed. The patient was immediately transfused with 2,000 cc. of blood. A chest roentgenogram two days later revealed no increase of the blood in the right pleural cavity. Two weeks after the initial thoracentesis, a repeat thoracentesis was performed and 200 cc. of dark-brown fluid

TABLE 1

Summary of Findings in 11 Cases of Benign Spontaneous Hemopneumothorax

CASE NUMBER	INITIALS	AGE	SEX	SIDE	LEVEL OF BLOOD	DURATION OF HEMOPNEUMOTHORAX	TOTAL LEUKOCYTE COUNT	SEDIMENTATION RATE	COMPLICATION	FOLLOW-UP
		years				*days*				
1	J. H.	44	M	Left	Ninth posterior rib	80	10.3	—	Thrombophlebitis of leg	Well 6 years
2	J. M.	31	M	Left	Ninth posterior rib	50	5.8	—	Thrombophlebitis of leg	Well 8 years
3	A. H.	36	M	Left	Seventh posterior rib	41	5.8	19	Underweight approx. 20 pounds	Well 1 year
4	D. K. E.	27	M	Right	Ninth posterior rib	730	15.0	48	Underweight approx. 30 pounds	None
5	W. G. S.	38	M	Right	Eleventh posterior rib	75	9.8	2	Underweight approx. 45 pounds	Well 1½ years
6	W. L. S.	30	M	Left	Eleventh posterior rib	38	19.5	5	Underweight approx. 31 pounds	Well 13 months
7	R. K.	21	M	Right	Seventh posterior rib	23	6.7	25	Normal weight	Well 1 year
8	J. J. D.	23	M	Right	Fourth posterior rib	90	3.6	—	Underweight 15 pounds; required decortication	Well 2 years
9	D. S.	20	M	Left	?	63	—	—	Developed small right spontaneous pneumothorax at same time; had two more spontaneous pneumothoraces on right but no spontaneous hemopneumothorax	Well 8 years
10	J. B.	20	M	Left	?	25	—	—	None	Well 3 years
11	J. G. C.	27	M	Right	Eighth posterior rib	22	15.1	—	None	Well 11 months
12	T. C. N.	21	M	Right	Ninth posterior rib	30	7.5	—	Underweight 40 pounds	None

were aspirated. The right lung expanded nicely as seen on serial chest roentgenograms and full re-expansion was apparent on the film of December 1, 1950. Both lungs were entirely clear at this time. At time of discharge, the hemoglobin was 16.4 gm. per 100 cc. Except for one day of fever up to 101° F., the course was afebrile, and the patient felt well during his entire stay. He requested that he be permitted to go home practically daily, because he felt so well. The discharge diagnosis was benign idiopathic spontaneous hemopneumothorax on the right with complete re-expansion of the right lung and full recovery.

A summary of the findings of the above described 12 cases of benign spontaneous hemopneumothorax may be seen in table 1.

SUMMARY

Twelve cases of benign spontaneous hemopneumothorax are reported. All of the patients recovered and are well without any evidence of pulmonary tuberculosis.

Spontaneous hemopneumothorax is not rare and is not usually fatal if treated promptly and actively.

Benign spontaneous hemopneumothorax is a variation of benign idiopathic spontaneous pneumothorax. The type of patient is the same: a male, twenty to forty years of age, fifteen to forty-five pounds underweight but otherwise well, who, while at rest or mild activity, suddenly develops a sharp, severe, unilateral, anterior chest pain. With hemopneumothorax, the patient is much more likely to be dyspneic and to be in shock.

Treatment is directed towards the general condition of the patient and his thoracic ailment. Transfusions and thoracenteses may be indicated.

SUMARIO

Hemoneumotórax Espontáneo Benigno

Esta exposición comprende 12 casos de hemoneumotórax espontáneo benigno. Todos los enfermos se repusieron y se hallan bien, sin el menor signo de tuberculosis pulmonar.

El hemoneumotórax espontáneo no es raro y no suele ser mortal, si es tratado pronta y activamente.

El hemoneumotórax espontáneo benigno representa una variación del neumotórax espontáneo idiopático benigno. El tipo del enfermo es idéntico: varón, de 20 a 40 años de edad, de 7 a 20 kg. bajo peso, pero bien en otros sentidos, que, mientras se encuentra en reposo o ligeramente ocupado, experimenta de repente un intenso y agudo dolor unilateral en la porción anterior del tórax. Cuando se trata de hemoneumotórax, es mucho más probable que el enfermo muestre disnea y se halle en estado de choque.

El tratamiento va dirigido al estado general del sujeto y a la dolencia torácica, pudiendo estar indicadas transfusiones y toracocéntesis.

RESUME

Hémopneumothorax spontané bénin

Douze cas d'hémopneumothorax spontané bénin sont rapportés. Tous les malades ont guéri, ils se portent bien et ne présentent pas de signes de tuberculose pulmonaire.

L'hémopneumothorax spontané n'est pas exceptionnel et n'est pas habituellement fatal s'il est traité rapidement et activement.

L'hémopneumothorax spontané est une variété de pneumothorax spontané idiopathique bénin. Le type de malade est le même, il s'agit d'un homme de 20 à 40 ans, dont le poids est d'environ 6 kg. 800 à 18 kg. 600 au-dessous de la normale, mais par ailleurs bien portant, qui, soit au repos soit au cours d'un exercice modéré éprouve soudain une douleur aiguë, intense, au niveau de la région thoracique antérieure. Lorsqu'il s'agit d'un hémopneumothorax le malade est plus apte à se montrer dyspnéique et en état de shock.

Le traitement est dirigé vers l'état général du malade et sa lésion pulmonaire. Les transfusions et la thoracentèse peuvent être indiquées.

Acknowledgment

Cases 8 and 11 are reported through the courtesy of Dr. Roger O. Egeberg, Clinical Director, Wadsworth General Hospital, West Los Angeles, California.

REFERENCES

(1) Dorset, V. J. and Terry, L. L.: Spontaneous hemopneumothorax with recovery, Am. J. Med., 1949, *6*, 135.
(2) Crimm, P. D.: Spontaneous collapse, J. Thoracic Surg., 1948, *17*, 662.
(3) Hartzell, H. C.: Spontaneous hemopneumothorax: Report of three cases and review of the literature, Ann. Int. Med., 1942, *17*, 496.
(4) Helwig, F. C., and Schmidt, E. C. H.: Fatal spontaneous hemopneumothorax: Review of the literature and report of a case, Ann. Int. Med., 1947, *26*, 608.
(5) Hyde, B., and Hyde, L.: Benign idiopathic spontaneous pneumothorax: A review of 63 cases, Am. J. M. Sc., 1948, *215*, 427.
(6) Rottenberg, L. A., and Golden, R.: Spontaneous pneumothorax: A study of 105 cases, Radiology, 1949, *53*, 157.
(7) Hansen, J. L.: Spontaneous pneumothorax, Acta med. Scandinav., 1949, *132*, 517.
(8) Solovay, J.: Spontaneous hemopneumothorax: Etiological considerations and case report, Radiology, 1949, *53*, 256.
(9) Hyde, B., and Hyde, L.: Tuberculous spontaneous pneumothorax, Am. Rev. Tuberc., 1949, *59*, 619.
(10) Tillett, W. S., and Sherry, S.: The effect in patients of streptococcal fibrolysin (streptokinase) and streptococcal desoxyribonuclease on fibrinous, purulent, and sanguineous pleural exudations, J. Clin. Investigation, 1949, *28*, 173.
(11) Sherry, S., Tillett, W. S., and Read, C. T.: The use of streptokinase-streptodornase in the treatment of hemothorax, J. Thoracic Surg., 1950, *20*, 393.

NEOMYCIN IN CLINICAL TUBERCULOSIS[1]

DAVID T. CARR, KARL H. PFUETZE, HENRY A. BROWN, BRUCE E. DOUGLASS, AND ALFRED G. KARLSON

(Received for publication November 29, 1950)

INTRODUCTION

The announcement of the discovery of neomycin by Waksman (1) in March 1949 was received with interest by students of the chemotherapy of tuberculosis, since Waksman stated in his original communication that the new drug was effective against streptomycin-resistant tubercle bacilli. He also reported that tubercle bacilli did not become resistant to the action of neomycin as rapidly as they became resistant to streptomycin. This report raised the hope that neomycin might replace, or at least supplement, streptomycin in the antibacterial treatment of tuberculosis. Clinical trials of the new drug were delayed, however, by difficulties encountered in producing a potent, nontoxic preparation, containing a single neomycin (2).

Late in 1949 the writers obtained supplies of neomycin[2] containing 160 and 200 Waksman units per milligram, which was said to be a single neomycin as determined by paper chromatograms. Experimental studies with this material revealed that it was effective against tuberculosis in guinea pigs produced by inoculation with either streptomycin-sensitive or streptomycin-resistant tubercle bacilli (3). The only demonstrable toxic effect was slight damage to the kidneys.

In view of these findings, it seemed reasonable to investigate the clinical effects of this preparation of neomycin in certain selected cases of tuberculosis.

PLAN OF INVESTIGATION

The preparation of neomycin containing 200 Waksman units per milligram was used in this study. The material was given to 6 patients, of whom 5 had tuberculosis due to streptomycin-resistant tubercle bacilli, and one had far advanced tuberculosis of the lungs and a carcinoma of the uterus with widespread metastases. The neomycin was dissolved in sufficient saline solution so that 1 cc. contained 200 mg. The drug was given intramuscularly at twelve-hour intervals, the total daily dose varying from 0.5 to 2.0 gm. The significant details of these cases are given in table 1. The patient of Case 4 died on the forty-first day of treatment. In all other cases, treatment was stopped because of toxic reactions.

RESULTS

Toxic Reactions

Only one patient complained of soreness in the muscle following injection of the drug, and the discomfort was not severe enough to require any change in

[1] From the Division of Medicine, Section on Otolaryngology and Rhinology, Mayo Clinic; the Mineral Springs Sanatorium, Cannon Falls, Minnesota; and the Mayo Foundation, Rochester, Minnesota.

[2] The neomycin used in this investigation was generously supplied by Dr. H. R. Hailman, The Upjohn Company, Kalamazoo, Michigan.

the regimen of treatment. Repeated studies of the blood and of the function of the liver revealed no evidence of damage to either of these systems. In all 6 patients, however, urinalyses and studies of the function of the kidneys provided evidence of damage to the kidneys. The patient of Case 6 had the greatest impairment of renal function, the concentration of the urea in the blood rising from a pretreatment value of 26 mg. per 100 cc. of blood to 52 mg. during treatment. At the same time the urea clearance decreased from a pretreatment value of 65.5 cc. per minute to 15.2 cc. per minute. However, the renal function rapidly

TABLE 1

Summary of the Significant Data Obtained During the Treatment of 6 Tuberculous Patients with Neomycin

CASE	AGE AND SEX	WEIGHT	DOSE OF NEOMYCIN,* GM. PER 12 HOURS	DURATION	SYMPTOMATIC IMPROVEMENT	CHANGE IN THORACIC ROENTGENOGRAM	DEAFNESS	NEOMYCIN SENSITIVITY OF TUBERCLE BACILLI IN UNITS PER CC.†	
								Before treatment	After treatment
		kg.		days					
1	51M	45.5	0.25 0.5	14 30	Yes	None	Severe	0.25	0.125
2	46F	47.3	0.25 0.5	14 30	No	None	None	0.25	0.125
3	46M	62.2	0.25 0.5	14 30	Yes	None	None	0.25	0.25
4	77M	43.4	0.25 0.5	14 27	Died	Worse	Moderate	0.5	1,024.0‡ (kidney)
5	41F	43.0	0.25 0.5	14 38	No	Worse	Moderate	0.25	0.25
6	34F	61.6	0.5 1.0	16 13	Yes	Improved	Severe	0.5	0.5

* The neomycin used had a potency of 200 Waksman units per milligram.

† In units per cubic centimeter of culture medium needed to inhibit growth completely.

‡ Tubercle bacilli from other organs had a sensitivity of 1.0 unit per cc. or less.

recovered when administration of neomycin was stopped. Post-mortem examination of the kidneys of another patient (Case 4), performed by Dr. A. H. Baggenstoss, revealed extensive necrosis and sloughing of the tubular epithelium with incomplete regeneration, all segments of the nephron being involved. Many of the tubules were filled with eosinophilic casts and cellular debris. The casts were especially prominent in the distal segments and the collecting tubules. The glomeruli appeared normal except for slight endothelial proliferation in the tufts. There was no evidence of tuberculosis of the kidneys.

The most important toxic reaction, however, was the sudden development of deafness in 4 of the 6 patients during the fourth to the sixth week of treatment.

This progressed to almost complete deafness in spite of the fact that treatment with neomycin was discontinued immediately. Audiograms (Case 6) made before and after treatment with neomycin are reproduced in figure 1.

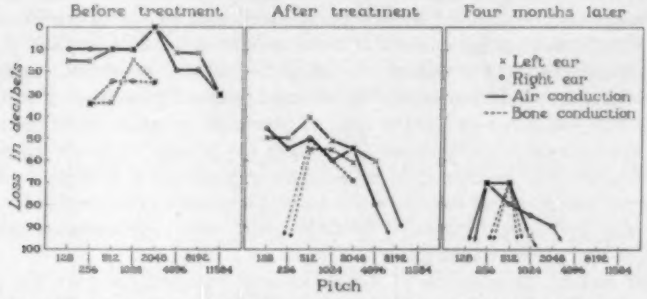


FIG. 1. Audiograms (Case 6) before and after treatment with neomycin, showing the development of deafness during treatment and its progression after the treatment was discontinued.

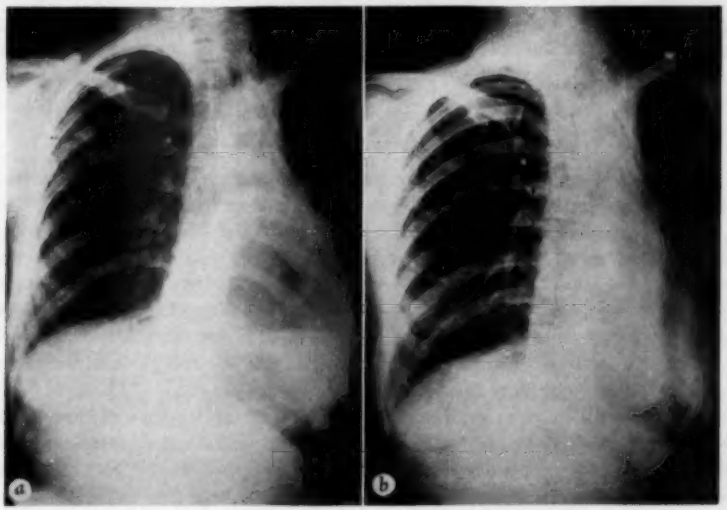


FIG. 2. Thoracic roentgenograms (Case 6) before (*a*) and after (*b*) treatment with neomycin for twenty-nine days, showing the resolution of the tuberculous bronchopneumonia at the level of the second anterior interspace on the right. Another roentgenogram four months later showed no further change.

Therapeutic Efficacy

Three of the 6 patients reported symptomatic improvement during the period of neomycin treatment. The improvement consisted of a decrease in cough and

the expectoration of a smaller amount of sputum. In one instance (Case 6), the patient's cough cleared completely and she ceased to expectorate anything. The first 3 patients had chronic bilateral fibrocavernous tuberculosis, and roentgenographic evidence of improvement was not to be expected. The thoracic roentgenograms of the other 3 patients revealed soft lesions of recent origin. Serial thoracic roentgenograms of 2 of these patients showed progression of their disease; one died during treatment, the other died several weeks after treatment when neomycin was discontinued. The roentgenograms of the chest of the sixth patient, who was given the largest dose of neomycin, revealed rapid resolution of the tuberculous bronchopneumonia during the month of treatment and a roentgenogram four months later revealed no evidence of a relapse (figure 2). Prior to treatment, direct smears of this patient's sputum were positive for acid-fast bacilli. Following treatment, tubercle bacilli were demonstrated only by culture of the gastric washings.

A post-mortem examination in the fourth case was performed by Dr. A. H. Baggenstoss and revealed fibrocaseous tuberculosis of both lungs with cavitation in the right upper lobe. There was tuberculosis of the right main bronchus, the peribronchial lymph nodes, the ileum and colon, the liver and the spleen. Histologically, there were fibrocaseous tuberculosis of both lungs and numerous daughter tubercles with central caseation, suggesting extensive progression. The lesions of the bronchus and intestines were also active and progressive. There was no evidence of healing such as is usually seen following treatment with streptomycin.

Neomycin Resistance

The neomycin sensitivity of the tubercle bacilli recovered from these patients before, during, and after treatment was determined, using Proskauer and Beck liquid medium containing 10 per cent horse serum.[3] Twofold dilutions of neomycin were used ranging from 32.0 Waksman units down to 0.25 Waksman unit per cubic centimeter of medium. Previous studies of 18 strains of human tubercle bacilli had revealed that all were sensitive to 0.5 unit or less of neomycin per cubic centimeter of culture medium. Tubercle bacilli from each of the 6 patients were equally sensitive before treatment. All of the microorganisms recovered during and after treatment were also sensitive except in Case 4. Tubercle bacilli recovered at post-mortem examination from one of the kidneys of this patient were found to be resistant to neomycin in a concentration of 1,024 units per cubic centimeter of culture medium. Tubercle bacilli recovered from the lungs, spleen, liver, and omentum, however, were found to be sensitive to 1.0 unit or less of neomycin per cubic centimeter of culture medium.

Concentration of Neomycin in the Blood Serum

Extensive studies of the absorption, distribution, and excretion of neomycin were not carried out. Nevertheless, the concentration of neomycin in the blood

[3] The method for preparing this medium has been described previously by Youmans and Karlson, Am. Rev. Tubere., 1947, *55*, 529.

serum at various intervals following the administration of the drug was determined by Dr. F. R. Heilman, using the cup plate method, the *SM Staphylococcus* being the test organism. The results of the studies are given in tables 2 and 3.

The bacteriostatic potency against a strain of virulent tubercle bacilli of blood serum of 5 of the patients was measured in samples drawn sixty or ninety minutes after the intramuscular injection of 0.25 or 0.5 gm. of neomycin. Each specimen of serum was serially diluted with Proskauer and Beck medium containing 10 per cent horse serum, so that dilutions of 1:1 through 1:256 were

TABLE 2

Concentration of Neomycin in the Blood Serum of 2 Patients Receiving 0.5 Gm. or 100,000 Units Intramuscularly Every Twelve Hours*

CASE	HOURS AFTER LAST INJECTION				
	1	2	4	8	12
4	8.8	8.4	8.5	5.3	2.95
5	3.83	3.75	2.73	0.7	Trace

* In Waksman units per cubic centimeter of blood serum.

TABLE 3

*Results of in Vitro Tests Measuring the Antibacterial Potency of the Blood Serum of Patients Receiving Neomycin**

CASE	DOSE OF NEOMYCIN	TIME†	CONCENTRATION OF NEOMYCIN IN SERUM‡	DILUTION OF SERUM						
				Control	1:8	1:16	1:32	1:64	1:128	1:256
	gm.									
1	0.25	60	2.4	4§	0	3	4	4	4	4
2	0.25	60	1.65	4	0	1	4	4	4	4
3	0.25	60	2.0	4	0	2	2	4	4	4
4	0.5	90	8.8	4	0	0	0	1	1	4
5	0.5	90	3.8	4	0	1	1	2	4	4

* Note that a concentration of 0.25 to 0.5 unit per cubic centimeter of diluted serum was required to inhibit growth completely.

† In minutes between injection of neomycin and collection of blood.

‡ In Waksman units per cc.

§ Amount of growth; 4 equals maximal growth, 0 equals no growth.

obtained. Tubes containing 4 cc. of the serially diluted serums were inoculated with 0.1 mg. of the H37Rv strain of tubercle bacilli. After fourteen days of incubation it was found that no growth had occurred in any of the tubes containing serum in the dilutions of 1:1 through 1:8. The amount of growth in the tubes containing greater dilutions of the serums is detailed in table 3. The concentration of neomycin in these serums is also given in the same table.

COMMENT

There can be no doubt that neomycin in sufficiently large doses is a potent antibacterial agent against the tubercle bacillus in experimental tuberculosis in

animals. Moreover, in the present study, suggestive indications of antimicrobial effect were observed in the one patient (Case 6) who received the largest daily dose (2.0 gm.) of the drug. In this case the lesion had developed while the patient was on a program of rest in bed following pneumonectomy for tuberculosis one year earlier. It is doubtful whether more rest would have resulted in such rapid subsidence of her cough and expectoration and resolution of the lesion as was seen in the serial thoracic roentgenograms. The other 5 patients, who received a smaller dose of neomycin, had only symptomatic benefit at best and the postmortem examination in the fourth case revealed no evidence of suppression of the disease. This finding is difficult to explain in view of the fact that an *in vitro* test revealed that the serum from this patient completely inhibited the growth of tubercle bacilli even in a dilution of 1:32.

The toxic reactions to neomycin are of much greater significance and would render the particular preparation of the drug studied of little or no clinical value in tuberculosis even if the smaller doses used in this investigation were therapeutically effective. Whether the toxic reactions were due to neomycin itself or to something else in the material is not known. Neither is it known why 2 of the patients did not become deaf. The difference in daily dose per kilogram of body weight does not seem sufficient to account for their escape. It is possible, however, that the difference between the safe and the toxic concentrations of neomycin in the blood serum may be small, and it will be noted that the 2 patients who did not become deaf (Cases 2 and 3) had the lowest concentration of neomycin in the blood serum (table 3).

The recovery of neomycin-resistant tubercle bacilli from one of the kidneys of the fourth patient after forty-one days of treatment suggests that neomycin-resistant strains of tubercle bacilli emerge as readily as is the case with streptomycin. This phenomenon alone probably would not be a serious disadvantage, for it is reasonable to assume that the concurrent administration of another antibacterial agent would delay or prevent the emergence of the resistant strains.

SUMMARY

Five patients with tuberculosis due to streptomycin-resistant tubercle bacilli and one patient with tuberculosis and carcinomatosis were treated with 0.25 to 1.0 gm. of neomycin containing 200 Waksman units per milligram every twelve hours for twenty-nine to fifty-two days.

Only 3 of the patients reported symptomatic benefit and in only one of these was there roentgenographic evidence of improvement.

All 6 patients had signs of renal damage which was transient. Progressive deafness developed in 4 patients.

Neomycin-resistant tubercle bacilli were recovered from a kidney of one patient who died after forty-one days of treatment.

SUMARIO Y CONCLUSIONES

La Neomicina en la Tuberculosis Clínica

Cinco enfermos con tuberculosis debida a bacilos tuberculosos estreptomicinorresistentes y uno con tuberculosis y carcinomatosis fueron tratados con 0.25

a 1.0 gm. de neomicina que contenía 200 unidades Waksman por mg., cada doce horas por espacio de veintinueve a cincuenta y dos días.

Sólo 3 de los enfermos comunicaron beneficio sintomático y sólo en uno de éstos había signos roentgenográficos de mejoría.

Los 6 enfermos manifestaron signos de lesión renal, pero ésta fué pasajera. En 4, se presentó sordera progresiva.

De uno de los riñones de un paciente que murió al cabo de cuarenta y un días de tratamiento, se obtuvieron bacilos tuberculosos neomicinorresistentes.

RESUMEN

La néomycine dans la tuberculose clinique

Cinq malades atteints de tuberculose à bacilles tuberculeux streptomycino-résistants et un malade atteint de tuberculose et de cancer ont été traités par la néomycine contenant 200 unités Waksman par mg. avec des doses de 0,25 à 1 g. toutes les douze heures pendant vingt-neuf à cinquante-deux jours.

Des résultats symptomatiques favorables n'ont été constatés que chez 3 malades seulement; et l'amélioration des signes radiologiques n'a été observée que chez un seul d'entre eux.

Chez ces 6 malades on a observé des signes temporaires d'altération du rein. Un surdité progressive s'est manifestée chez 4 malades.

Des bacilles tuberculeux néomycino-résistants ont été trouvés, dans un des reins, chez un malade ayant succombé au bout de quarante et un jours de traitement.

REFERENCES

(1) Waksman, S. A., and Lechevalier, H. A.: Neomycin, a new antibiotic active against streptomycin-resistant bacteria, including tuberculosis organisms, Science, 1949, *109*, 305.

(2) Hobby, G. L., Lenert, T. F., and Dougherty, N.: The evaluation of neomycin and other antimicrobial agents of bacterial and fungal origin, and substances from higher plants, Ann. New York Acad., Sc., 1949, *52*, 775.

(3) Karlson, A. G., Gainer, J. H., and Feldman, W. H.: Neomycin in experimental tuberculosis of guinea pigs, Dis. of Chest, 1950, *17*, 493.

THE TUBERCULOSTATIC ACTIVITY OF TERRAMYCIN[1]

GLADYS L. HOBBY, TULITA F. LENERT, MARY DONIKIAN, AND DARIA PIKULA

(Recieved for publication July 31, 1950)

INTRODUCTION

Terramycin is a new antimicrobial agent which has been investigated widely during the past year (1–8). Its possible value as an antituberculous agent was first mentioned in an early communication from this laboratory (2) in which it was reported that terramycin is capable of inhibiting the growth of both streptomycin-sensitive and streptomycin-resistant strains of *M. tuberculosis in vitro*. Subsequent reports from this laboratory (9) and by Steenken and Wolinsky (10, 11, 12) have confirmed these observations and have indicated further that terramycin is also capable of suppressing tuberculous infection in experimentally inoculated mice and guinea pigs.

The present report is designed to clarify the available evidence concerning the antituberculous activity of this new antibiotic.

MATERIALS AND METHODS

Partially purified and crystalline preparations of terramycin and its salts were used throughout the study. The methods used have been described in detail elsewhere (2, 13, 14). An incubation period of seven days was used in all sensitivity tests, unless otherwise specified; this short period was used in view of the fact that the antibiotic loses a portion of its potency when incubated at 37° C. for longer periods.

RESULTS

In Vitro Activity

Sensitivity to terramycin: The sensitivities, *in vitro*, of a number of human strains of tubercle bacilli to terramycin and its salts are illustrated in table 1. Four to 16 γ of pure terramycin per ml. of medium were sufficient to inhibit growth of these strains under the conditions described. Based on comparative sensitivity tests in the presence and in the absence of Tween 80, it is apparent that this substance does not influence significantly the sensitivity of the organism to terramycin and its salts. That terramycin is probably no more active against tubercle bacilli, *in vitro*, than aureomycin is illustrated in table 2. Terramycin is active against both streptomycin-sensitive and streptomycin-resistant strains (2, 9–12).

The activity of terramycin against streptomycin-resistant strains of *M. tuberculosis* early suggested the possibility that terramycin might be especially effective when used in combination with streptomycin or other antituberculous

[1] From the Research Laboratories, Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

agents. *In vitro* studies, carried out to determine the activity of terramycin under such conditions, have shown that subinhibitory concentrations of terramycin, equivalent to one-fifth to one-tenth of the amount required for inhibition of growth, significantly decrease the concentrations of streptomycin, viomycin, and aureomycin necessary for inhibition of growth. The effect upon the concen-

TABLE 1

Comparison of the Antituberculous Activity of Terramycin and Its Salts in Vitro

STRAIN OF *M. tuberculosis*	TERRAMYCIN			
	Amphoteric	HCl	SO_4	Sodium
	Sensitivity: γ per ml. at 7 days (37°C.)			
H37Rv				
Isolate #2678	8	8	8	8
Freshly Isolated				
Sta.*	8	8	8	5
Mun	5	8	5	4
Bel	8	8	8	8
Nit	8	8	8	8
Mos	16	8	8	—

Dubos liquid medium containing 0.02 per cent Tween 80 and 0.5 per cent albumin used throughout.

* Sta. is a streptomycin-resistant strain.

TABLE 2

Comparison of Antituberculous Activity of Terramycin and Aureomycin in Vitro

STRAIN OF *M. tuberculosis*	SENSITIVITY: γ PER ML. AT 7 DAYS (37°C.)	
	Terramycin HCl	Aureomycin HCl
H37Rv		
Isolate #2678	10	10
Freshly Isolated		
Mund.*	3	8
Mun	8	12
Nit	8	10
Mar	8	8
Sti	3	8

Dubos liquid medium containing 0.02 per cent Tween 80 and 0.5 per cent albumin used throughout.

* Mund. is a streptomycin-resistant strain.

trations of chloramphenicol or penicillin necessary for inhibition of growth was less pronounced. No alteration in the amount of neomycin required for inhibition of growth was observed (table 3).

Resistance to terramycin: Terramycin is a bacteriostatic agent which exerts a bactericidal effect only if high concentrations are used (2, 15). Organisms resistant to its action emerge from otherwise sensitive strains at an exceedingly

slow rate. Indeed, none of the 5 strains of *M. tuberculosis* tested showed any significant increase in resistance during twelve transfers in liquid medium which contained subinhibitory concentrations of terramycin (table 4).

TABLE 3

The Antituberculous Activity of Terramycin Alone and in Combination with Other Antimicrobial Agents

STRAIN	CONCENTRATION OF TERRAMYCIN	SENSITIVITY TO:						
		VM*	SM	TM	NM	AM	CM	PEN
	γ per ml.	γ per ml.			units per ml.	γ per ml.		units per ml.
H37Rv #2678	0	3.1	0.6	12.5	0.6	25	20	640
	0.12	3.1	0.4		0.8	25	20	640
	0.25	2.5	0.4		0.8	20		320
	0.63	2.5	0.4		0.8	20	20	400
	1.25	1.6	0.3		1.2	10	10	400
	2.50	1.6	0.16		0.8	6	10	160
Mun.	0	5.0	0.6	12.5	1.2	20	25	640
	0.12	3.1	0.6		1.2	25	25	400
	0.25	3.1	0.4		1.2	25	25	320
	0.63	(5.0)	0.4		1.2	25	20	640
	1.25	3.1	0.4		1.6	20	10	320
	2.50	1.6	0.16		1.6	20	12	400
Mund.	0	5.0	80	12.5	2.5	40	20	400
	0.12	3.1	12.5		1.2	40	20	400
	0.25	5.0				40	20	320
	0.63	5.0	12.5		1.2	40	20	
	1.25	1.6	12.5		1.6	40	10	320
	2.50	1.2	12.5		1.2	20	3	100
Sta.	0	3.1	3,200	12.5		25	25	640
	0.12	5.0	200			25	25	640
	0.25	2.5	100			20	25	640
	0.63	3.1	50			25	25	640
	1.25	6.0	100			20	12	640
	2.50	1.2	25			10	6	400

* Symbols indicate viomycin (VM), streptomycin (SM), terramycin (TM), neomycin (NM), aureomycin (AM), chloramphenicol (CM), penicillin (PEN).

In Vivo Activity

Chemotherapeutic action: Studies to determine the chemotherapeutic action of terramycin against tuberculous infection were carried out in mice infected intracerebrally according to the methods described previously (13, 14). In a rapidly

TABLE 4

The Rate of Emergence of Resistance to Terramycin and Streptomycin in Vitro (M. tuberculosis)

STRAIN	ANTIBIOTIC	SENSITIVITY: γ PER ML.			
		Number of Transfers			
		1	4	8	12
H37Rv (#2290)	Terramycin	100	125	125	125
	Streptomycin	2.0	>200	>1,000*	
MeV.	Terramycin	100	125	125	125
	Streptomycin	0.5		50	>1,000*
Mos.	Terramycin	100	125	125	125
	Streptomycin	1.0		50	>1,000*
Mund.	Terramycin	100	125	(125)†	(250)†
	Streptomycin	100	>1,000*		
Mun.	Terramycin	100		125	125
	Streptomycin	2.0	>10	>1,000*	

* This degree of resistance was reached on fifth (#2290), tenth (MeV.), tenth (Mos.), fourth (Mund.), and seventh (Mun.) transfers, respectively.

† On seventh transfer, sensitivity was equivalent to 250 γ per ml. while on eleventh transfer it was equivalent to only 125 γ per ml.

Readings were made after an incubation period of fourteen to eighteen days, which accounts for the low initial sensitivity of these strains, in contrast to that illustrated in tables 1 and 2.

TABLE 5

The Chemotherapeutic Action of Terramycin and Its Sodium Salt against Experimental Tuberculosis in Mice

FORM OF TERRAMYCIN	DAILY DOSAGE (MG. PER 20-GRAM MOUSE)	ROUTE OF ADMINISTRATION	AVERAGE SURVIVAL TIME (DAYS)				PER CENT SURVIVAL			
			Observation Days				Observation Days			
			30	60	90	180	30	60	90	180
Amphoteric	8.6	Subcutaneous	27	48	66	120	70	60	60	60
	4.3	Subcutaneous	25	39	47	105	70	40	20	0
	2.4	Subcutaneous	20	32	44	64	40	40	40	30
	2.8	Oral	28	46	52	69	90	20	20	10
	Controls	—	24	24	24	24	0	0	0	0
Sodium	2.2	Subcutaneous	30	58	84	156	100	90	80	80
	1.1	Subcutaneous	27	47	62	107	80	50	50	50
	Controls	—	30	36	36	36	70	0	0	0

progressing infection, in which the average survival time of the untreated control animals was 24 days, a dosage equivalent to 8.6 mg. of terramycin per 20-gram mouse per day was sufficient to increase the average survival time to 120 days, a fivefold increase in average survival time. Lower dosages of the sodium salt of terramycin, equivalent to 1.1 to 2.2 mg. per day, were sufficient to cause an approximately three- to four-fold increase in survival time. Terramycin, both in its amphoteric form and its sodium salt, was effective in suppressing this infection. Preliminary observations have suggested that terramycin hydrochloride, when administered subcutaneously, may be slightly less effective.

DISCUSSION

The development of streptomycin and the recognition of its value as a chemotherapeutic agent in tuberculosis has aroused interest in an evaluation of the potentialities of other antibiotics in the treatment of this infection. The frequency with which organisms resistant to the action of streptomycin emerge from otherwise sensitive strains has remained a serious drawback to its use and the need for other antituberculous agents capable of acting upon streptomycin-resistant strains is well recognized. The activity of terramycin *in vitro* and *in vivo* against streptomycin-resistant strains of tubercle bacilli and its low toxicity suggest that this agent may be of value in this regard.

It is apparent from the data reported herein that terramycin is less active than streptomycin. Nonetheless, it is also apparent that it does possess activity which cannot be ignored. It is difficult to say how potent a compound should be, under experimental conditions *in vitro* or *in vivo*, to justify its trial clinically.

The close similarity between aureomycin and terramycin and the lack of demonstrated activity of aureomycin as an antituberculous agent cast some doubt on the possibility that terramycin will be effective against human tuberculosis. It should be noted, however, that the dosage of terramycin which proved effective in the present study was appreciably higher than the dosage of aureomycin used in the reported studies with experimental or clinical tuberculosis.

The dosages of terramycin used in this study were 430 and 55 to 110 mg. per kg. of body weight of mouse per day of the amphoteric form and the sodium salt of terramycin, respectively, administered by the subcutaneous route. The limited data reported herein on the effect of orally administered terramycin, as well as the known ratio between parenteral and oral dosages of terramycin capable of producing comparable concentrations in the serum and tissues (3, 4), indicate that even higher dosages would be necessary to produce a significant antituberculous effect with orally administered terramycin.

Steenken and Wolinsky (16) used 3.2 mg. of aureomycin per kg. of body weight per day, by the intramuscular route, for forty-eight days in experimental tuberculosis in guinea pigs, while Perry (17) carried out similar experiments using a dosage of 10 mg. per kg. per day subcutaneously for forty-two days. In Rake and Donovick's studies (18) in mice infected with the Ravenel strain of *M. tuberculosis*, the aureomycin dosage was 100 mg. per kg. of body weight per day by the oral route. No chemotherapeutic responses were observed in any of these studies.

Steinbach and his associates (19) and Schwartz, Walton, and Moyer (20) used dosages of 1.5 to 4 gm. daily in patients with tuberculosis and reported failure of this drug to alter the course of tuberculous infection in man.

In view of the results reported herein with terramycin, it would seem that one of three possibilities exist: (*1*) aureomycin and terramycin differ significantly in antituberculous activity; (*2*) inadequate dosages of aureomycin have been used to permit demonstration of an antituberculous action; (*3*) the degree of tuberculostatic activity of terramycin, although sufficient to exert an effect upon the course of experimental tuberculosis in mice and guinea pigs, is insufficient to alter the course of the human disease. Evidence against the last-named possibility is presented by Tempel and others (21) who recently reported preliminary observations on the treatment of a small number of patients receiving 7 gm. daily by the oral route for a period of 120 days. In this report he also called attention to the potential value of terramycin when used in combination with other antimicrobial agents against streptomycin-resistant strains of *M. tuberculosis*.

SUMMARY

Terramycin, a new antibiotic of broad antimicrobial activity and low toxicity, is capable of inhibiting the growth of both streptomycin-sensitive and streptomycin-resistant strains of tubercle bacilli. The antituberculous activity was observed both *in vitro* and *in vivo*. Tubercle bacilli resistant to the action of terramycin emerge from otherwise sensitive cultures at an exceedingly slow rate.

SUMARIO

La Actividad Tuberculostática de la Terramicina

La terramicina, neuvo antibiótico dotado de amplia actividad antimicrobiana y de poca toxicidad, se ha mostrado capaz de inhibir la proliferación de las cepas tanto estreptomicinosensibles cuanto estreptomicinorresistentes de los bacilos tuberculosos. Es activa *in vitro* e *in vivo*. Dótala aun de mayor interés el hecho de la suma lentitud con que surgen microbios resistentes a sus efectos de cultivos por lo demás sensibiles.

RESUME

Activité de la Terramycine dans la tuberculose

La terramycine, un nouvel antibiotique possédant une activité antimicrobienne étendue et une faible toxicité, est capable d'inhiber le développement des souches streptomycino-sensibles et streptomycino-résistantes du bacille tuberculeux. Cet antibiotique est actif *in vitro* et *in vivo*. Il offre un intérêt particulier en raison du fait que l'apparition de germes résistant à son action est excessivement lente à se produire dans des cultures qui, par ailleurs, sont sensibles à son action.

REFERENCES

(1) Finlay, A. C., Hobby, G. L., P'an, S. Y., Regna, P. P., Routien, J. B., Seeley, D. B., Shull, G. M., Sobin, B. A., Solomons, I. A., Vinson, J. W., and Kane, J. H.: Terramycin, a new antibiotic, Science, 1950, *111*, 85.

(2) HOBBY, G. L., DOUGHERTY, N., LENERT, T. F., HUDDERS, E., AND KISELUK, M.: Antimicrobial action of terramycin *in vitro* and *in vivo*, Proc. Soc. Exper. Biol. & Med., 1950, *73*, 503.

(3) HOBBY, G. L., REED, W., RINNE, D., POWERS, M., AND D'AMBROSIA, A.: Absorption and excretion of terramycin in animals, Proc. Soc. Exper. Biol. & Med., 1950, *73*, 511.

(4) WELCH, H., HENDRICKS, F. D., PRICE, C. W., AND RANDALL, W. A.: Pharmacologic action of terramycin, J. Am. Pharm. A., Sc. ed., 1950, *39*, 185.

(5) HERRELL, W. E., HEILMAN, F. R., WELLMAN, W. E., AND BARTHOLOMEW, L. H.: Terramycin: Some pharmacologic and clinical observations, Proc. Staff Meet., Mayo Clin., 1950, *25*, 183.

(6) HENDRICKS, F. D., GREAVES, A. B., OLANSKY, F., TAGGART, S. R., LEWIS, C. N., LANDMAN, G. S., MACDONALD, G. R., AND WELCH, H.: Terramycin in the treatment of venereal disease, J. A. M. A., 1950, *143*, 4.

(7) KING, E. Q., LEWIS, C. N., WELCH, H., CLARK, E. A., JOHNSON, J. B., LYONS, J. B., SCOTT, R. B., AND CORNELY, P. B.: Clinical observations following the use of terramycin hydrochloride, J. A. M. A., 1950, *143*, 1.

(8) Proceedings of Conference on Terramycin, held under the auspices of The New York Academy of Sciences, Ann. N. Y. Acad. Sc., 1950, *53*, 221–460.

(9) HOBBY, G. L.: The tuberculostatic activity of terramycin and viomycin. Presented at the Ninth Streptomycin Conference held by the Veterans Administration, St. Louis, Mo., April 19, 1950. Tr. Ninth Streptomycin Conference, April 1950, p. 92.

(10) STEENKEN, W., JR.: *In vivo* and *in vitro* antituberculous activity of terramycin and viomycin. Presented at the Ninth Veterans Administration Conference on Tuberculosis, April 19, 1950. Tr. Ninth Streptomycin Conference, April 1950, p. 189.

(11) STEENKEN, W., JR., AND WOLINSKY, E.: The tuberculostatic action of terramycin *in vitro* and in the experimental animal, Proc. Conf. on Terramycin, Ann. N. Y. Acad. Sc., 1950, *53*, 309.

(12) STEENKEN, W., JR., AND WOLINSKY, E.: Effects of antimicrobial agents on the tubercle bacillus and on experimental tuberculosis, Am. J. Med., 1950, *9*, 633.

(13) HOBBY, G. L., LENERT, T. F., DONIKIAN, M., AND PIKULA, D.: The activity of viomycin against *Mycobacterium tuberculosis* and other microorganisms *in vitro* and *in vivo*, Am. Rev. Tuberc., 1951, *63*, 17.

(14) HOBBY, G. L., LENERT, T. F., AND DOUGHERTY, N.: Evaluation of neomycin and other antimicrobial agents of bacterial and fungal origin, and substances from higher plants, Ann. N. Y. Acad. Sc., 1949, *52*, 775.

(15) HOBBY, G. L., LENERT, T. F., PIKULA, D., KISELUK, M., AND HUDDERS, M. E.: The antimicrobial action of terramycin, Proc. Conf. on Terramycin, Ann. N. Y. Acad. Sc., 1950, *53*, 266.

(16) STEENKEN, W., JR., AND WOLINSKY, E.: Tuberculostatic activity of aureomycin *in vitro* and *in vivo*, Am. Rev. Tuberc., 1949, *59*, 221.

(17) PERRY, T. L.: Failure of aureomycin in the treatment of experimental tuberculosis, Proc. Soc. Exper. Biol. & Med., 1949, *72*, 45.

(18) RAKE, G., AND DONOVICK, R.: Tuberculostatic activity of aureomycin *in vitro* and *in vivo* (letter to the editors), Am. Rev. Tuberc., 1949, *60*, 143.

(19) STEINBACH, M. M., DOONEIEF, A. S., AND BUCHBERG, A. S.: The use of aureomycin in pulmonary tuberculosis, Am. Rev. Tuberc., 1949, *59*, 624.

(20) SCHWARTZ, W. S., WALTON, S. T., AND MOYER, R. E.: Aureomycin in the treatment of tuberculosis, Am. Rev. Tuberc., 1950, *61*, 875.

(21) TEMPEL, C. W., HUGHES, F. J., MARDIS, R. E., AND DYE, W.: Terramycin in the treatment of tuberculosis. Proc. Tenth Conference on Chemotherapy of Tuberculosis, held under the auspices of the Veterans Administration, Army and Navy, January 1951 (in press, 1951).

THE CHEMOTHERAPY OF ACTINOMYCOSIS AND NOCARDIOSIS[1,2]

RICHARD E. STRAUSS, ALBERT M. KLIGMAN[3], AND DONALD M. PILLSBURY

(Received for publication November 20, 1950)

INTRODUCTION

The fungi which are classified under the Actinomycetes are an uncommon cause of human disease. The Actinomycetes may be thought of as the bacteria-like fungi. Three clinical entities have been attributed to this group of organisms: actinomycosis, nocardiosis, and maduromycosis.

Actinomycosis, strictly speaking, is caused by *Actinomyces bovis*. The best known feature is the discharge of "sulfur granules" in the pus draining from the sinuses characteristic of this condition. Actinomycosis may be fatal.

Nocardiosis is a rare pulmonary disease caused by *Nocardia asteroides* (1, 2). It may resemble tuberculosis. *Nocardia asteroides* shows striking morphologic and antigenic relationships to *Mycobacterium hominis* (3).

Maduromycosis (mycetoma, Madura foot) is a rare disease characterized by multiple nodules, grotesque enlargement of the foot, and sinus tracts in which "fungus granules" are discharged. Several cases have been reported in the United States (4). Approximately one-half of the cases which have been investigated bacteriologically have been due to species of *Nocardia* (other than asteroides). The other causative species are distributed among ten genera.

The advent of the newer chemotherapeutic agents has greatly facilitated the treatment of this group of diseases. Actinomycosis has responded favorably to large doses of penicillin and the sulfonamide drugs (5). Recently a good clinical response has been reported with aureomycin (6).

The majority of patients with nocardiosis in the pre-chemotherapeutic era succumbed to the disease. Sulfonamides have been life saving in some cases (2).

Amputation of the involved part is required in many cases of maduromycosis. The newer antibiotics, however, have not been adequately studied in cases of mycetoma due to species of *Nocardia*.

The Actinomycetes are the only fungi which are susceptible to the common chemotherapeutic agents. This undoubtedly results from the close relationship of this group to the bacteria. The hyphae which make up the vegetative phase of the pathogenic Actinomycetes are extremely slender filaments of bacterial dimensions. These filaments are divided by repeated septation into chains of bacillary or coccoid-like cells. These, when separated from the chain, closely resemble certain types of bacilli.

There are two aspects to the present study: (*1*) the *in vitro* susceptibility of

[1] From the Department of Dermatology and Syphilology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] The studies reported in this paper were in part supported by U. S. Army Grant No. W-49-007-MD-473.

[3] Senior Research Fellow, National Institutes of Health, Public Health Service.

representative species of pathogenic Actinomycetes to various chemotherapeutic drugs; and (2) the effect of drugs on experimental nocardiosis in mice.

MATERIALS AND METHODS

Culture techniques: Three strains of *Actinomyces bovis* were grown in thioglycolate broth. Two were isolated from human infections and one from a bovine infection. The chemotherapeutic agents were dissolved in appropriate dilutions in tubes of thioglycolate broth. The tubes were then inoculated with 0.1 cc. of broth containing the actively growing organisms. Growth in the tubes was compared with a control growth after ten days of incubation at 37°C.

Ten strains of *Nocardia asteroides* and one strain each of *N. mexicanus*, *N. madurae*, *N. purpureum*, and *N. hemolyticus* were cultured on Sabouraud agar medium. The strains

TABLE 1

Inhibition of Actinomyces Bovis by Chemotherapeutic Agents

(γ per cc.)

Drug	Strain 1 (human)		Strain 2 (human)		Strain 3 (bovine)	
	P*	C†	P	C	P	C
Aureomycin	50	100	20	—‡	50	100
Chloramphenicol	5	10	<1	20	2	10
Penicillin	50	—	<1	1	<1	50
Streptomycin	20	200	20	50	2	10
Neomycin	50	200	50	200	—	—
Sodium sulfadiazine	—	—	—	—	200	—
Diasone	—	—	—	—	—	—
Promin	—	—	—	—	—	—
Myvisone	—	—	—	—	20	—
N,N-bis (thiocarbamyl) hydrazine	—	—	—	—	—	—
Para-aminosalicylic acid	—	—	200	—	20	200

* Partial inhibition.

† Complete inhibition.

‡ Indicates more than 200 γ per cc.

other than *N. asteroides* had been isolated from cases of mycetoma. Known concentrations of the drugs to be tested were dissolved in Sabouraud medium in Petri dishes. The various *Nocardia* were then streaked onto the Petri dishes. The plates were incubated at 37°C. and read after six to eight days.

Murine infection: A lethal infection with *Nocardia asteroides* was produced in mice by injecting a suspension of a measured quantity of the organism in a 5 per cent solution of hog gastric mucin. Without the mucin the strains used do not cause death in mice. Details of this procedure have been outlined in another communication (7).

To produce lethal infections with *N. asteroides*, it was necessary to inject intraperitoneally 0.5 cc. of a 1:60 volumetric suspension of the organism in 5 per cent gastric mucin. This was followed in six hours and then at daily intervals by an intraperitoneal injection of one of the drugs which had seemed to be of most value *in vitro*. White Swiss mice were used. A group of uninfected mice were given daily intraperitoneal injections of each of the drugs to determine whether the drugs were of themselves toxic. The drugs were given for a period of three days.

Antimicrobial drugs: The drugs used were: (1) the antibiotics: aureomycin, chloramphenicol

col, penicillin, streptomycin, terramycin, neomycin, bacillomycin, and actidione; (*2*) sodium sulfadiazine; (*3*) the antituberculous drugs: para-aminosalicylic acid and Myvizone (*p*-formylacetanilide thiosemicarbazone); (*4*) the antileprous drugs: Diasone and Promin; and (*5*) N,N-bis (thiocarbamyl) hydrazine. The last named agent has been found to have a substantial fungistatic effect *in vitro* against some of the fungi which characteristically produce deep-seated infections (8).

TABLE 2

Inhibition of Nocardia Asteroides by Chemotherapeutic Agents

(γ per cc.)

	Strain 1		Strain 2		Strain 3		Strain 4		Strain 5		Strain 6		Strain 7		Strain 8		Strain 9		Strain 10	
	P*	C†	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Aureomycin	2	10	10	10	2	10	10	10	10	10	<1	<1	2	10	2	10	20	50	10	10
Chloramphenicol	10	20	50	100	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Penicillin	200	—‡	—	—	200	—	—	—	—	—	50	—	200	—	50	—	100	200	—	—
Streptomycin	—	—	—	—	—	—	20	100	50	100	20	100	—	—	—	—	100	—	100	200
Neomycin	—	—	—	—	—	—	—	—	—	—	50	—	—	—	—	—	—	—	—	—
Terramycin	§	§	100	100	50	50	50	100	50	100	50	100	50	100	<1	20	100	100	20	100
Bacillomycin	—	—	—	—	—	—	—	—	—	—	100	—	—	—	—	—	—	—	—	—
Actidione	—	—	—	—	—	—	—	—	—	—	20	—	100	—	—	—	—	—	—	—
Sodium sulfadiazine	50	—	200	—	50	200	50	200	100	—	10	50	200	—	200	—	50	200	50	—
Diasone	—	—	—	—	50	—	200	—	200	—	50	100	—	—	—	—	100	—	—	—
Promin	—	—	—	—	—	—	—	—	—	—	20	—	—	—	—	—	50	—	50	—
Myvisone	<1	10	50	200	<1	<1	100	—	<1	—	2	10	<1	<1	§	§	<1	200	<1	50
Para-aminosalicylic acid	10	200	200	—	10	—	100	200	—	—	10	100	10	200	10	200	—	—	10	200
N,N-bis (thiocarbamyl) hydrazine	20	20	20	50	20	50	20	50	10	20	10	10	10	10	10	10	10	50	10	50

* Partial inhibition.

† Complete inhibition.

‡ Indicates more than 200 γ per cc.

§ No growth in control culture.

RESULTS

Studies in vitro: In table 1 may be seen the inhibition of growth of *Actinomyces bovis* obtained with eleven different chemotherapeutic agents. The most active drugs were the antibiotics, aureomycin, chloramphenicol, penicillin, and streptomycin. Neomycin, in high concentrations, inhibited two of the three strains tested. The three strains of *A. bovis* exhibited marked variation in their susceptibility to the same chemotherapeutic agent. On the whole, chloramphenicol gave the best results.

Tables 2 and 3 show the inhibition of various *Nocardia* by fourteen chemotherapeutic agents. Aureomycin, chloramphenicol, terramycin, Myvisone, and N,N-bis (thiocarbamyl) hydrazine were effective against all of the strains tested.

TABLE 3

Inhibition of Four Species of Nocardia by Chemotherapeutic Agents

(γ per cc.)

DRUG	*N. mexicana*		*N. madurae*		*N. purpurea*		*N. hemolytica*	
	P*	C†	P	C	P	C	P	C
Aureomycin	10	50	<1	<1	<1	<1	<1	<1
Chloramphenicol	20	100	20	50	2	10	10	10
Penicillin	—‡	—	20	—	1	2	2	200
Streptomycin	100	200	50	50	10	10	10	20
Neomycin	—	—	<1	100	<1	50	2	—
Terramycin	10	100	10	10	<1	<1	20	20
Bacillomycin	—	—	—	—	—	—	—	—
Actidione	—	—	—	—	—	—	—	—
Sodium sulfadiazine	10	50	200	—	50	—	200	—
Diasone	200	—	—	—	—	—	—	—
Promin	—	—	—	—	—	—	—	—
Myvizone	—	—	<1	50	50	—	—	—
Para-aminosalicylic acid	—	—	200	—	200	—	—	—
N,N-bis (thiocarbamyl) hydrazine	10	10	20	—	20	200	50	200

* Partial inhibition.

† Complete inhibition.

‡ Indicates greater than 200 γ per cc.

TABLE 4

Effect of Chemotherapeutic Agents on Survival Rate of Mice Infected with Nocardia Asteroides

	DAILY DOSAGE (MG. PER KG.)	NUMBER OF MICE INJECTED	DEATHS AFTER DAY					SURVIVAL RATIO
			1	2	3	4	5	
Control	—	36	26	10	—	—	—	0/36
Sodium sulfadiazine	10	18	2	1	1	0	0	14/18 (78 per cent)
Sodium sulfadiazine	25	18	3	0	0	1	0	14/18 (78 per cent)
Sodium sulfadiazine	50	18	0	0	0	0	0	18/18 (100 per cent)
Sodium sulfadiazine	100	18	0	0	0	0	0	18/18 (100 per cent)
Aureomycin	25	18	2	8	8	—	—	0/18
Aureomycin	50	18	3	2	3	2	0	8/18 (44 per cent)
Aureomycin	75	18	0	3	4	3	2	6/18 (33 per cent)
Chloramphenicol	25	18	2	1	1	5	0	9/18 (50 per cent)
Chloramphenicol	50	18	4	14	—	—	—	0/18
Terramycin	25	18	1	9	8	—	—	0/18
Terramycin	50	18	1	12	5	—	—	0/18
Myvizone	2	18	8	3	0	0	1	6/18 (33 per cent)
N,N-bis (thiocarbamyl) hydrazine	100	18	16	2	—	—	—	0/18

Sodium sulfadiazine showed at least partial inhibition of all the strains. Its fungistatic effect was not striking in comparison to some of the antibiotics. Penicillin, streptomycin, Diasone, and para-aminosalicylic acid gave partial to

complete inhibition of several of the strains of *Nocardia asteroides*. Streptomycin was fairly effective against the strains of *Nocardia* other than asteroides, while penicillin and neomycin were somewhat less effective.

Studies in vivo: As shown in table 4, all the untreated control animals receiving *Nocardia asteroides* in gastric mucin were dead in two days. None of the uninfected mice receiving the drugs (drug controls) died. N,N-bis (thiocarbamyl) hydrazine seemed to have no appreciable effect on prolonging the life of the mice. Terramycin given in daily dosages of 25 mg. and 50 mg. per kg. of body weight was associated with a slight lengthening of the survival time, but all of the mice given the drug were dead within three days. Chloramphenicol in the daily dosage of 25 mg. per kg. enabled one-half of the treated mice to survive. A dosage of 50 mg., however, resulted in the death of all of the animals in two days. With a daily dosage of 25 mg. of aureomycin per kg., all of the mice succumbed in three days. Larger dosages of 50 and 75 mg. per kg. protected 33 to 44 per cent of the mice. Sodium sulfadiazine in 50- and 100-milligram dosages protected all of the mice while smaller quantities of the drug still gave a large degree of protection.

To determine whether the route of administration of the drugs had any effect on experimental nocardiosis, a group of 12 mice was given intraperitoneal injections of *Nocardia asteroides* of a 1:40 concentration in gastric mucin. The amount of water the mice drank daily was determined. Sodium sulfadiazine was then dissolved in the drinking water and given to the infected mice so that they would get approximately 80 mg. per kg. of body weight per day. After five days, only 2 of the 12 infected mice had succumbed to the infection. Twelve animals which received a similar injection of *Nocardia asteroides* without sulfadiazine in the drinking water were all dead within two days.

A lethal infection in the chick embryo may be produced by inoculating the chorio-allantoic membrane with a 1:1,000 concentration of *Nocardia asteroides*. In a preliminary study with 200 infected eggs, sodium sulfadiazine enabled the embryos to survive and diminished the number of plaques formed. Aureomycin and chloramphenicol afforded little or no protection. This corresponds to the results of the studies in mice.

DISCUSSION

The strains of *Actinomyces bovis* tested *in vitro* showed marked variation in their response to chemotherapeutic agents. There have been similar findings in several human cases of actinomycosis (5). For this reason, it is exceedingly important to determine the *in vitro* susceptibility of a particular isolate before therapy is begun. The sensitivity to aureomycin, chloramphenicol, penicillin, and streptomycin should be evaluated in every case. In view of the chronicity of the disease, combined therapy with several agents may be indicated.

Variation in susceptibility was not as striking with the strains of *Nocardia* tested. There was enough variation, however, to warrant sensitivity studies in clinical cases. Certainly the *in vitro* sensitivity to sulfonamides, aureomycin, and chloramphenicol should be determined.

The results obtained with various drugs in protecting mice with nocardiosis were clear cut. Sodium sulfadiazine was by far the drug of choice and in doses of

moderate size protected all of the animals. This corresponds to clinical experience. It should be noted that strain 7 which was used for this experiment was relatively insensitive to sulfadiazine *in vitro*. This discrepancy between *in vitro* and *in vivo* results stresses the decisive value of animal studies in chemotherapeutic investigations.

Aureomycin in larger dosages enabled a substantial number of infected mice to survive. Chloramphenicol gave encouraging results when a dosage of 25 mg. per kg. was given, but doubling this dose resulted in the death of all of the animals. A daily dose of 50 mg. in uninfected animals was well tolerated. It must be assumed that the drug has sufficient toxicity in this dosage range which, when associated with the *Nocardia* infection, produced death.

Myvisone afforded an appreciable degree of protection in the dosage given. Since 2 mg. per kg. of body weight per day of the drug is the recommended human dosage, larger quantities than this were not given to the mice. Although terramycin did delay death in some of the mice for one day, its value in human infections seems questionable. N,N-bis (thiocarbamyl) hydrazine had no noticeable *in vivo* effect, the drug apparently being inactivated in the body.

It should be pointed out that all of the infected mice which survived as a result of drug therapy had numerous peritoneal lesions. No significance was attached to the failure of the drugs to prevent lesions since a comparable pathologic response was seen in mice inoculated with dead organisms. A foreign-body response is evidently elicited.

Throughout the experiment the drugs were given once daily. This method of administration undoubtedly failed to maintain adequate concentrations in the blood in some cases. Greater protection might have been afforded if certain of the antibiotics had been given in divided doses. This might well be the case with aureomycin and chloramphenicol which proved highly effective *in vitro* and only partially effective *in vivo*. It is possible that these two drugs might prove to be as effective as the sulfonamides in the treatment of human nocardiosis.

Attempts to produce satisfactory experimental mouse infections with *Actinomyces bovis* by suspending the organisms in gastric mucin were unsuccessful. This precluded animal studies. Meyer and her co-workers, however, have been able to produce intraperitoneal nodules in mice by using gastric mucin (9).

SUMMARY

The inhibiting potentialities of various chemotherapeutic agents against three strains of *Actinomyces bovis*, ten strains of *Nocardia asteroides*, and one strain each of *Nocardia mexicanus*, *Nocardia madurae*, *Nocardia purpureum*, and *Nocardia hemolyticus* were tested *in vitro*.

Marked variation was noted in the susceptibility of the three strains of *Actinomyces bovis*. The most active drugs against the organism were, in order of their effectiveness, chloramphenicol, penicillin, streptomycin, and aureomycin. The performance of *in vitro* sensitivity determinations is regarded as essential for the proper therapy of fungal infections in humans.

The various species of *Nocardia* were inhibited to the greatest extent by aureo-

mycin, chloramphenicol, terramycin, Myvizone, and N,N-bis (thiocarbamyl) hydrazine. Sodium sulfadiazine was moderately effective *in vitro* against all of the strains tested.

In animal protection tests against nocardiosis, sodium sulfadiazine provided almost perfect protection, enabling 100 per cent of infected mice to survive. Aureomycin, chloramphenicol, and Myvizone gave only partial protection.

SUMARIO

La Quimioterapia de la Actinomicosis y la Nocardiosis

Comprobáronse *in vitro* las potencialidades inhibidoras de varias sustancias quimioterapéuticas contra tres cepas de *Actinomyces bovis*, diez de *Nocardia asteroides*, y una cada una de *Nocardia mexicanus*, *Nocardia madurae*, *Nocardia purpureum* y *Nocardia hemolyticus*.

Notóse decidida variación en la susceptibilidad de las tres cepas de *Actinomyces bovis*. En el orden de su efectividad, las drogas más activas contra dicho microbio fueron: cloranfenicol, penicilina, estreptomicina y aureomicina. Las determinaciones de la sensibilidad resultan imperativas en la terapéutica humana.

Las varias especies de *Nocardia* fueron inhibidas en mayor grado por la aureomicina, el cloranfenicol, la terramicina, la mivizona y la N,N-bis (tiocarbamilo) hidracina. La sulfadiacina sódica se mostró moderadamente eficaz *in vitro* contra todas las cepas comprobadas.

En los estudios de la protección de los animales contra las nocardiosis, la sulfadiacina otorgó protección casi perfecta, permitiendo que sobrevivieran 100 por ciento de los ratones infectados. La aureomicina, el cloranfenicol y la mivizona sólo suministraron protección parcial.

RESUME

La Chimiothérapie de l'actinomycose et de la Nocardiose

Le potentiel d'inhibition offert par les divers agents chimiothérapiques contre trois souches d'Actinomyces-bovis, dix souches de *Nocardia-astériodes* et respectivement une souche de *Nocardia mexicanus*, *Nocardia madurae*, *Nocardia pupureum* et *Nocardia hemolyticus* a été éprouvé *in vitro*.

Des variations de sensibilité des trois souches *d'Actinomyces bovis* ont été notées. Les substances les plus actives contre ces microorganismes ont été par ordre d'efficacité: le chloramphénicol, la pénicilline, la streptomycine et l'auréomycine. Les épreuves de sensibilité sont considérées aussi impératives en thérapie humaine.

Les diverses espèces de *Nocardia* ont été inhibées à un degré considérable par l'auréomycine, le chloramphénicol, la terramycine, la myvizone, et le N,N-bis (thiocarbamyl) hydrazine. La sulfadiazine sodique s'est montrée modérément efficace contre toutes les souches, dans les tests *in vitro*.

Dans les recherches sur la protection de l'animal contre la nocardiose, la sulfadiazine sodique a assuré une protection presque parfaite, elle a permis la survie de 100 pour cent des souris inoculées. L'auréomycine, le chloramphénicol et la myvizone n'ont procuré qu'une protection partielle.

REFERENCES

(1) HAGER, H. F., MIGLIACCIO, A. V., AND YOUNG, R. M.: Nocardiosis; pneumonia and empyema due to *N. asteroides*, New England J. Med., August 11, 1949, *241*, 226.

(2) TUCKER, F. C., AND HIRSCH, E. F.: Nocardiosis with a report of 3 cases of actinomycosis due to *Nocardia asteroides*, J. Infect. Dis., 1949, *85*, 72.

(3) FREUND, J., AND LIPTON, M.: Potentiating effect of *Nocardia asteroides* on sensitization to picryl chloride and on production of isoallergic encephalomyelitis, Proc. Soc. Exper. Biol. & Med., 1948, *68*, 373.

(4) REILLY, E. B., AND STEEL, H. H.: Mycetoma: Report of a case of actinomycotic variety, New England J. Med., December 8, 1949, *241*, 900.

(5) DOBSON, L., AND CUTTING, W.: Penicillin and sulfonamides in the therapy of actinomycosis, J.A.M.A., July 21, 1945, *128*, 856.

(6) WRIGHT, L. T., AND LOWEN, H. J.: Aureomycin hydrochloride in actinomycosis, J.A.M.A., September 2, 1950, *144*, 21.

(7) STRAUSS, R. E., AND KLIGMAN, A. M.: The use of gastric mucin to lower resistance of laboratory animals to systemic fungus infections, J. Infect. Dis. (in press).

(8) TAGER, M., AND DANOWSKI, T. S.: Inhibition of fungi by thiourea derivatives, particularly hydrazine dithiocarbamyl, J. Infect. Dis., 1948, *82*, 126.

(9) MEYER, E., VERGES, P., AND NOVAK, M. V.: Mouse pathogenicity as a diagnostic aid in the identification of *Actinomyces bovis*, Proceedings of Annual Meeting of Society of American Bacteriologists (Abstract), 1950, 114.

THE DEMONSTRATION OF STREPTOMYCIN-RESISTANT TUBERCLE BACILLI IN NECROPSY SPECIMENS[1]

EDGAR M. MEDLAR, SIDNEY BERNSTEIN, AND
FREDRIC C. REEVES

(Received for publication December 29, 1950)

INTRODUCTION

The emergence of resistance to streptomycin in the population of *M. tuberculosis* in patients who are administered this antiobiotic is a common occurrence provided that a sufficient amount of the antibiotic is given over a period of several weeks. This phenomenon can be demonstrated readily by direct cultures of random samples of sputum on solid medium to which streptomycin has been added. The change and the time of its appearance in the bacterial population with regard to an ability to grow in the presence of streptomycin varies considerably from patient to patient in the proportion of the population that evidences a change, in the degree of change which occurs, and with the amount of the antibiotic which has been given. It is not known, however, that the phenomenon observed in random samples of sputum reflects the status of the entire bacterial population harbored by the tuberculous patient.

There are only meager reports of cultures taken at necropsy from tuberculous lesions. Fisher (1) reports that no visible lesions were found which contained sensitive bacilli only in cultures of material from six necropsies on patients who had received streptomycin for at least 120 days. From ten samples of tuberculous lesions from three necropsies, Saenz and Canetti (2) found considerable variation in the resistance of *M. tuberculosis* to streptomycin in different types of lesions. They suggest that these differences may be due to the difference in the blood supply to the lesions. No reference has been found relative to similar studies from necropsies of persons who had not received streptomycin therapy. To obtain information regarding the status of the bacterial population within lesions, samples from tuberculous foci which represent different phases in pathogenesis were obtained at necropsy for bacteriologic study, and the present report presents the data obtained from fifteen necropsies on tuberculosis patients.

PROCEDURE

Before organs were incised to obtain material for culture, they were thoroughly rinsed in running water and prior to each incision the knife was thoroughly cleansed in running water. The freshly incised edges were carefully retracted, and sterile cotton swabs were used to obtain material for study. If a cavity was small its content was sampled and, if large, different areas of the inner surface of the cavity were rubbed with sterile cotton swabs and the material that adhered was used for study. In necrotic lesions with friable contents,

[1] From the Veterans Administration Hospital, Sunmount, New York.

the grumous material was lifted out with a sterile swab, and in solid necrotic or non-necrotic pneumonic lesions samples of tissue were cut out with a cleansed knife and placed in sterile Petri dishes. Samples were obtained from both lungs and from necrotic lesions in other organs whenever possible. It is believed that the essential difference between the various lesions which were sampled rests upon the amount of necrosis and of slough that has occurred and upon the age of the lesion. From the fifteen necropsies, ninety-six samples were obtained.

The samples of tissue were ground with sterile sand in a mortar to obtain minute fragments suitable for digestion and concentration. All samples were treated in the manner recommended (3) for the preparation of sputum samples for culture. The concentrated sediment was planted directly by capillary pipettes in aliquot portions on two tubes of the solid medium used routinely in this laboratory (3) and on one tube each of solid medium which contained 3.5, 15, and 200 γ of streptomycin per ml. of medium after inspissation (4). Final reading of cultures was made at the end of six weeks and all data on cultures recorded in this paper concern the results of the final reading.

The data on the cultures in each case are presented, together with the age, sex, and race of the patient; hours post mortem of performance of the necropsy; the lapse of time between the end of the antibiotic therapy and death; the data on cultures prior to and after completion of antibiotic therapy relative to resistance to streptomycin; and the amount of chemotherapeutic agent given. All of the samples tested are regarded as random samples and no attempt was made to quantitate the volume of each sample. Generally the grumous contents from necrotic lesions and the samples of tissue exceeded considerably the volume of material adhering to the cotton swabs dipped into the fluid contents or rubbed over the inner surface of cavities.

In recording the amount of growth in culture tubes the following scheme was used: less than 50 colonies were recorded numerically; 1 plus, 50 to 100 colonies per tube; 2 plus, more than 100 discrete colonies; 3 plus, colonies so numerous as to be confluent in some areas; 4 plus, confluent growth over entire surface.

The pertinent data on each case are presented in table 1.

OBSERVATIONS

In table 2 is presented a comparison of the amount of growth obtained in all cases on the medium without streptomycin from the samples obtained from cavities and from other lesions. All specimens taken from cavities yielded growth of *M. tuberculosis*, and only 20 per cent showed less than 100 colonies per tube of medium. The samples from other lesions gave less than 100 colonies per tube of medium in 45 per cent, and an additional 15 per cent (all old necrotic foci) showed no growth. Thus 60 per cent of the unexcavated lesions yielded a sparse growth of bacilli for the amount of material which was planted. This agrees with microscopic study of tuberculous lesions. Bacilli usually are found easily in the inner surface of cavities, whereas commonly they are difficult to find in necrotic lesions, with the oldest necrotic foci usually containing the fewest organisms. Cultures from different areas of large cavities usually yielded comparable amounts of growth; however, a considerable variation in the amount of growth frequently was obtained from different cavities and from different unsloughed lesions. On occasion considerable difference existed between lesions in the two lungs of a single case.

The irregularity in the distribution of tubercle bacilli in lesions is a common

TABLE 1

Data on Patients and on Direct Cultures on Solid Medium with and without Streptomycin Added

Samples Obtained from Tuberculous Lesions at Necropsy

CASE NUMBER	AGE	SEX	RACE	CAUSE OF DEATH	HOURS POST MORTEM	GM. OF STREPTOMYCIN GIVEN	SURVIVAL AFTER THERAPY DISCONTINUED	SOURCE OF MATERIAL	SOLID MEDIUM WITH STREPTOMYCIN INCORPORATED			
									Micrograms streptomycin per ml.			
									None	3.5	15	200
1	24	M	W	Tuberculosis	17	1 gm. daily for 140 days	3 months	Pre-treatment sputum	Sensitive to 0.5 γ per ml. liquid medium			
								Post-treatment sputum	Sensitive to 125 γ per ml. liquid medium			
								Left lung:				
								Cavity (1)	2+	2+	1+	37*
								Cavity (2)	3+	3+	1+	6
								Cavity (3)	13	7	8	0
								Old necrotic lesion	0	0	0	0
								Right lung:				
								Cavity (1)	3+	3+	3+	1+
								Cavity (2)	4+	4+	3+	3+
								Necrotic peribronchial lymph node	3+	3+	Contaminated	Contaminated
								Old necrotic lesion	0	0	0	0
2	30	M	C	Tuberculosis	13	1 gm. daily for 182 days	8 months	Pre-treatment sputum	Sensitive to 0.5 γ per ml. liquid medium			
								Post-treatment sputum	Resistant to 1,000 γ per ml. liquid medium			
								Left lung:				
								Cavity (1)	3+	2+	2+	1+
								Cavity (2)	4+	4+	4+	4+
								Necrotic lesion	3+	3+	3+	2+
								Right lung:				
								Cavity (1)	3+	3+	2+	10
								Cavity (2)	4+	4+	3+	5
								Abscess (nontuberculous) appendix	0	0	0	0
3	32	M	W	Tuberculosis	5	1 gm. streptomycin and 6 gm. Promizole for 25 days	4½ months	Pre-treatment sputum	3+	0	0	0
								Post-treatment sputum	4+	4+	3+	3+
								Left lung:				
								Cavity	4+	4+	3+	2+
								Necrotic lesion (1)	4+	4+	2+	2+
								Necrotic lesion (2)	2+	30	5	3
								Necrotic lesion (3)	6	2	0	0
								Right lung:				
								Cavity (1) area (1)	4+	4+	4+	4+
								Cavity (1) area (2)	4+	4+	4+	4+
								Cavity (1) area (3)	4+	3+	3+	2+
								Cavity (1) area (4)	4+	4+	3+	3+
								Cavity (2)	4+	4+	4+	3+
								Necrotic lesion	1+	1+	10	13

TABLE 1—*Continued*

CASE NUMBER	AGE	SEX	RACE	CAUSE OF DEATH	HOURS POST MORTEM	GM. OF STREPTOMYCIN GIVEN	SURVIVAL AFTER THERAPY DISCONTINUED	SOURCE OF MATERIAL	SOLID MEDIUM WITH STREPTOMYCIN INCORPORATED			
									Micrograms streptomycin per ml.			
									None	3.5	15	100
4	39	M	C	Carcinoma of prostate with extensive metastases to lung	3	1 gm. dihydrostreptomycin and 5 gm. PAS daily for 25 days.	Died during therapy	Pre-treatment sputum	3+	0	0	0
								Sputum just prior to death	3+	0	0	0
								Left lung:				
								Cavity (sloughed CA)	0	0	0	0
								Necrotic lesion (1)	1	0	0	0
								Necrotic lesion (2)	0	0	0	0
								Right lung:				
								Cavity (1)	23	0	0	0
								Cavity (2) (sloughed CA)	0	0	0	0
								Old necrotic lesion	0	0	0	0
								Tracheobronchial lymph node	0	0	0	0
								Retrosternal lymph node	0	0	0	0
								Perisortic lymph node	0	0	0	0
5	54	M	W	Tuberculosis	14	1 gm. daily for 42 days	3½ months	Pre-treatment sputum	4+	4	0	0
								Post-treatment sputum	4+	4+	1+	17
								Left lung:				
								Cavity (1)	4+	4+	1	0
								Cavity (2)	35	25	0	0
								Cavity (3)	2+	1+	0	0
								Necrotic lesion	3+	3+	2+	2
								Right lung:				
								Old cavity	2	0	0	0
								Necrotic lesion	1+	2	0	0
								Necrotic prostatic focus	4+	4+	35	30
6	41	M	W	Tuberculosis	3	1 gm. daily for 84 days	8 months	Post-treatment sputum	4+	3+	2+	2+
								Left lung:				
								Cavity (area 1)	4+	4+	4+	4+
								Cavity (area 2)	4+	4+	4+	4+
								Cavity (area 3)	4+	4+	4+	4+
								Necrotic lesion (1)	2+	2+	2+	1+
								Necrotic lesion (2)	1+	20	10	10
								Necrotic lesion (3)	11	16	31	9
								Pre-necrotic lesion (1)	2+	2+	2+	1+
								Pre-necrotic lesion (2)	4+	4+	4+	4+
7	49	M	W	Tuberculosis	9	Aerosol streptomycin for 42 days; amount given unknown	24 months	Post-treatment sputum	3+	0	0	0
								Left lung:				
								Cavity	2+	0	0	0
								Necrotic lesion	1	0	0	0
								Right lung:				
								Cavity (1)	2	0	0	0
								Cavity (2)	35	0	0	0
								Cavity (3)	13	0	0	0
								Necrotic lesion (1)	1	0	0	0
								Necrotic lesion (2)	0	0	0	0

TABLE 1—*Continued*

CASE NUMBER	AGE	SEX	RACE	CAUSE OF DEATH	HOURS POST MORTEM	GM. OF STREPTOMYCIN GIVEN	SURVIVAL AFTER THERAPY DISCONTINUED	SOURCE OF MATERIAL	SOLID MEDIUM WITH STREPTOMYCIN INCORPORATED			
									Micrograms streptomycin per ml.			
									None	3.5	15	200
8	53	M	W	Tuberculosis	12	3 gm. intrapleurally over period of 6 days	12 months	Post-treatment sputum	4+	0	0	0
								Left lung:				
								Cavity	4+	30	0	0
								Necrotic lesion (1)	4+	0	0	0
								Necrotic lesion (2)	20	0	0	0
								Necrotic lesion (3)	4+	0	0	0
								Right lung:				
								Cavity	4+	1	0	0
								Necrotic lesion	4+	1+	0	0
9	52	M	W	Tuberculosis	12	1 gm. streptomycin daily for 130 days	13 months	Post-treatment sputum	4+	4+	3+	20
								Left lung:				
								Cavity	2+	2+	1+	35
								Necrotic lesion (1)	2+	0	0	0
								Necrotic lesion (2)	2+	2+	1+	1
								Necrotic lesion (3)	2+	2+	2+	3+
								Right lung:				
								Old necrotic lesion	4	3	0	0
								Necrotic lesion	18	7	0	0
10	32	M	W	Tuberculosis	7	1 gm. daily for 42 days	9 months	Pre-treatment sputum	4+	0	0	0
								Post-treatment sputum	4+	4+	3+	3+
								Left lung:				
								Cavity (1)	3+	3+	2+	2+
								Cavity (2)	3+	2+	20	35
								Necrotic lesion	2+	2+	45	45
								Right lung:				
								Cavity	1+	1+	15	15
								Necrotic lesion	1+	1+	1	0
11	60	M	W	Tuberculosis	6	None	—	*Left lung:*				
								Cavity	4+	0	0	0
								Necrotic lesion (1)	2+	0	0	0
								Necrotic lesion (2)	1+	0	0	0
								Right lung:				
								Old necrotic lesion	0	0	0	0
12	59	M	W	Tuberculosis	3	None	—	*Left lung:*				
								Cavity	3+	4	0	0
								Old necrotic lesion	0	0	0	0
								Right lung:				
								Necrotic lesion (1)	20	20	0	0
								Necrotic lesion (2)	25	0	0	0
								Old necrotic lesion	0	0	0	0
13	50	M	C	Tuberculosis	17	1 gm. daily for 120 days	16 months	Pre-treatment sputum	Sensitive to 0.5 γ per ml. liquid medium			
								Post-treatment sputum	Resistant to 1,000 γ per ml. liquid medium			
								Left lung:				
								Necrotic lesion (1)	1+	3	5	1
								Necrotic lesion (2)	5	3	1	0
								Necrotic lesion (3)	30	10	10	2
								Necrotic lesion (4)	30	20	15	20
								Right lung:				
								Cavity	2+	2+	2+	2+
								Necrotic peribronchial lymph node	2+	2+	2+	2+

TABLE 1—*Concluded*

CASE NUMBER	AGE	SEX	RACE	CAUSE OF DEATH	HOURS POST MORTEM	GM. OF STREPTOMYCIN GIVEN	SURVIVAL AFTER THERAPY DISCONTINUED	SOURCE OF MATERIAL	SOLID MEDIUM WITH STREPTOMYCIN INCORPORATED — Micrograms streptomycin per ml.			
									None	3.5	15	200
14	64	M	W	Tuberculosis	4	1 gm. daily for 84 days	15 months	Pre-treatment sputum	3+	0	0	0
								Post-treatment sputum	4+	4+	4+	4+
								Left lung:				
								Cavity (1)	4+	4+	4+	4+
								Cavity (2)	4+	3+	1+	10
								Necrotic lesion (1)	3+	1+	1+	10
								Necrotic lesion (2)	1+	15	15	3
								Right lung:				
								Cavity (1) area (1)	3+	3+	3+	3+
								Cavity (1) area (2)	3+	3+	3+	3+
								Cavity (1) area (3)	4+	4+	4+	4+
								Cavity (2)	4+	4+	4+	4+
								Cavity (3)	4+	3+	2+	2+
15	33	M	W	Tuberculosis	6	1 gm. daily for 120 days	35 months	Pre-treatment sputum	Sensitive to 0.5 γ per ml. liquid medium			
								Post-treatment sputum	Resistant to 1,000 γ per ml. liquid medium			
								Left lung:				
								Necrotic lesion	3+	1+	0	0
								Pre-necrotic lesion	35	0	0	0
								Right lung:				
								Cavity (1)	5	5	4	8
								Cavity (2)	1+	25	30	15
								Necrotic lesion	8	1	3	0
								Pre-necrotic lesion	15	35	18	15

Colonies per tube.

TABLE 2

Comparison of Amount of Growth on Medium without Streptomycin from Cavities and from Other Lesions

All Cases Included

SOURCE OF MATERIAL	NUMBER OF SAMPLES	AMOUNT OF GROWTH	
		Less than 100 colonies per tube	No growth
All cultures	96	32 (33.3 per cent)	8 (8.3 per cent)
Cavities	45	9 (20.0 per cent)	—
Other lesions	51	23 (45.1 per cent)	8 (15.7 per cent)

feature of the disease, and this phenomenon requires careful consideration in an interpretation of the phenomenon of resistance to a chemotherapeutic agent whenever samples are taken for culture from lesions which are representative of the different phases in the pathogenesis of the disease. Differences in the amount of bacterial growth were found in this study among persons who had received streptomycin as well as among those who had been given no antibiotic.

Ten of the patients had received 35 gm. or more of streptomycin over a period of five to twenty-four weeks, and five had received less than 25 gm. or none of

the antibiotic. In table 3 is presented a comparison between the two groups of patients and between cavity and other lesions relative to the phenomenon of bacterial resistance to streptomycin. It is apparent that there is a significant difference between the two groups of patients. In the comparison of lesions, due consideration was given to the probability of an uneven distribution of bacilli in the concentrate which was planted and, unless there was a marked disparity between the amount of growth on the medium with and without streptomycin, the growths were considered comparable. Thus in case 2 (table 1) the three cultures from the left lung were considered comparable on all tubes of medium with streptomycin to the growth on medium without streptomycin; whereas in the two cultures from the right lung the amount of growth on the medium which contained 200 γ of streptomycin per ml. was not considered to be comparable to growth on the medium without streptomycin.

In the group of cases which had received over 35 gm. of streptomycin, it appeared that resistance to this antibiotic was present in a higher proportion of the bacterial population and to a higher degree in cavity formations than in other lesions. This difference may be due to some extent to the smaller number of colonies often obtained from lesions which had not excavated. A comparison of equal quantities of bacilli from all lesions might have revealed less difference than seems to be present in the cultures from concentrates of specimens.

From the data in table 3, it appears that the bacterial population in all types of lesions is affected by the administration of more than 35 gm. of streptomycin; however, this effect is not uniform in all lesions. It can persist for a long time after the discontinuance of the antibiotic, e.g., Case 15 (table 1). Moreover, it appears that the phenomenon of bacterial resistance can develop in unsloughed necrotic lesions which from pathologic characteristics suggest that they were present prior to the administration of streptomycin. It has been demonstrated (5) that streptomycin can penetrate cavity "walls." On the basis of the structure of tuberculous lesions, there would seem to be no reason why streptomycin could not penetrate unsloughed necrotic lesions as readily as it does the "walls" of cavity formations. At necropsy one can only assume from the macroscopic appearance of pulmonary lesions that some necrotic lesions probably were present before the antibiotic was administered. The writers have had the opportunity to study a solid necrotic pulmonary lesion which was 2 cm. in diameter and which was surgically removed after daily doses of one-half gram of dihydrostreptomycin had been given for seventy days. Cultures obtained from deep within the necrotic debris gave as good growth of *M. tuberculosis* on medium which contained 200 γ of streptomycin as on the medium without streptomycin. This clearly shows that streptomycin can penetrate solid necrotic lesions.

The random cultures from necropsy specimens did not show an equal quantity of growth in all patients who had received streptomycin. In a comparison of the growth from sputum at the end of streptomycin therapy with the growth obtained from the necropsy specimens there is no evidence of a significant difference in the proportion of the bacterial population which was resistant to streptomycin. There was just as great a difference in the quantity of bacterial growth obtained

from necropsy specimens in persons who had received streptomycin as in those who had not received this antibiotic. It is our experience that the proportion of the bacterial population which becomes resistant to streptomycin can be of the same order in patients who show a decrease of the bacterial population in the sputum during therapy as in those who show either little change or an increase

TABLE 3

Comparison of Group of Cases Which Had Received More Than 35 Grams of Streptomycin with Those Which Had Received Less Than 25 Grams or No Antibiotic. Also Comparison of Growth on Tubes Which Contained Streptomycin with That on Tubes without Streptomycin from Cavities and Other Lesions

SOURCE OF MATERIAL	NUMBER OF CULTURES	GROWTH ON MEDIA WITH STREPTOMYCIN COMPARABLE* TO GROWTH WITHOUT STREPTOMYCIN		
		Amount of streptomycin per ml.		
		3.5 γ	15 γ	200 γ
10 cases—35 to 148 grams of streptomycin				
All cultures..	70 (100 per cent)	60 (85.7 per cent)	48 (68.5 per cent)	34 (48.5 per cent)
Cavities.....	36 (100 per cent)	35 (97.2 per cent)	29 (80.6 per cent)	22 (61.1 per cent)
Other lesions.....	34 (100 per cent)	25 (73.5 per cent)	19 (55.9 per cent)	12 (35.3 per cent)
5 cases—No streptomycin or up to 25 grams of streptomycin				
All cultures..	26 (100 per cent)	1 (4 per cent)	—	—
Cavities.....	9 (100 per cent)	—	—	—
Other lesions.....	17 (100 per cent)	1 (6 per cent)	—	—

* The cultures were obtained from the planting of aliquot portions of concentrates of specimens on media with and without streptomycin incorporated and in each specimen the amount of growth on the medium without streptomycin was used as the standard for comparison. On this basis the following criteria were used for comparable growths on media that contained different amounts of streptomycin:

2+ and 3+ comparable to 4+
1+ comparable to 2+ only
If 15 or more colonies are present, numerical growth comparable to 1+ only
If the ratio between the number of colonies on the tubes compared is not over 3:1, then numerical growths are comparable.

These criteria are arbitrary. However this procedure allows a condensed tabulation which demonstrates a considerable difference between the amount of growth on the medium without streptomycin when compared to the amount of growth on media that contains streptomycin in different concentrations.

in the bacterial population. These observations suggest that it is not the emergence of bacterial resistance which changes the ability of the patient to destroy tubercle bacilli. It appears that the basic biologic conditions which enable *M. tuberculosis* to thrive in the tissue of one person more than in another are not significantly affected by the administration of streptomycin. It seems probable that the major effect of this antibiotic concerns its ability to create an environ-

ment which at the time acts as a deterrent to bacterial growth. Once this environment is surmounted by *M. tuberculosis* the effectiveness of streptomycin is lost. However, this does not indicate necessarily that progression of the disease will occur promptly with the emergence of streptomycin-resistant organisms.

SUMMARY

Data are presented on 96 cultures from necropsy material of 10 persons who had received over 35 gm. of streptomycin and 5 persons who had received either no antibiotic or less than 25 gm.

Evidence of bacterial resistance to streptomycin was found in every patient who had received over 35 gm. of the antibiotic, whereas this phenomenon was not present in patients who had received either no antibiotic or less than 25 gm.

Evidence of bacterial resistance to streptomycin was found in unsloughed lesions as well as in cavity formation, although there seemed to have developed a higher proportion of the bacterial population which was resistant and a higher degree of resistance to streptomycin in sloughing lesions (cavities).

It appears that the bacterial population as a whole is affected by the administration of 35 gm. or more of streptomycin over a period of five weeks or longer, although there may be considerable difference in different lesions and in the two lungs in a patient.

The emergence of resistance to streptomycin need not enhance the ability of *M. tuberculosis* to thrive in tissues. However, once a considerable proportion of the bacterial population has become resistant, then streptomycin, per se, may no longer be an effective deterrent to bacillary growth.

SUMARIO

Descubrimiento de Bacilos Tuberculosos Estreptomicinorresistentes en Ejemplares Autópsicos

Los datos presentados versan sobre 96 cultivos obtenidos del material autópsico procedente de 10 personas que habían recibido más de 35 gm. de estreptomicina y de 5 que o bien no habían recibido antibiótico o habían recibido menos de 25 gm.

En todos los enfermos que habían recibido más de 35 gm. del antibiótico, observáronse signos de resistencia bacteriana a la estreptomicina, mientras que no existía dicho fenómeno en los que no habían recibido el antibiótico o recibido menos de 25 gm.

Descubriéronse signos de resistencia bacteriana a la estreptomicina en las lesiones no esfaceladas así como en las cavernas, aunque parecía haber una proporción mayor de la población bacteriana resistente y dotada de mayor resistencia a la estreptomicina en las lesiones esfaceladas (cavernas).

Parece que la población bacteriana en conjunto se ve afectada por la administración de 35 gm. o más de estreptomicina durante un período de cinco semanas o más, si bien puede haber considerable diferencia entre diversas lesiones y entre los dos pulmones del mismo enfermo.

RESUME

Présence de bacilles tuberculeux streptomycino-résistants dans les spécimens prélevés au cours d'autopsies

Les données fournies par 96 cultures provenant de matières prélevées après autopsie, chez 10 individus ayant reçu plus de 35 g. de streptomycine et de 5 individus n'ayant reçu aucun antibiotique, ou moins de 25 g., sont rapportées.

Des manifestations de résistance bactérienne à la streptomycine ont été découvertes chez tous ceux des sujets ayant reçu plus de 35 g. de l'antibiotique; ce phénomène était absent chez ceux n'ayant reçu aucun antibiotique, ou moins de 25 g.

Des manifestations de résistance à la streptomycine ont été trouvées aussi bien dans les lésions tissulaires non ulcérées que dans les lésions cavitaires, toutefois dans ces dernières les micro-organismes résistants étaient présents en plus grand nombre et la résistance à la streptomycine était plus marquée.

Il apparaît que l'administration de 35 g. de streptomycine ou plus influence la population bactérienne dans son ensemble pendant une période de cinq semaines ou plus; cependant, des différences appréciables entre les diverses lésions et entre les deux poumons s'observent chez un même malade.

REFERENCES

(1) Fisher, M. W.: Fitzsimons Army Hospital report on development of resistance. Veterans Administration, Minutes of the Fifth Streptomycin Conference, April 1948.

(2) Saenz, A., and Canetti, G.: La streptomycino-resistance du bacille de Koch en fonction de la dose de streptomycine administrée, Rev. de la tuberc., 1949, *13*, No. 9–10.

(3) American Trudeau Society: Report on the Committee on Evaluation of Laboratory Procedures, Am. Rev. Tuberc., 1946, *54*, 428.

(4) Bernstein, S., Bradley, E. M., Medlar, E. M., and Steenken, W., Jr.: Comparison of a liquid and a solid medium method for detection of streptomycin-resistant *Mycobacterium tuberculosis*, Am. Rev. Tuberc., 1950, *62*, 101.

(5) Steenken, W., Jr., D'Esopo, N. D., and Wolinsky, E.: Excretion of streptomycin into tuberculous cavities, the pleural space and the tracheobronchial tree, Am. Rev. Tuberc., 1947, *56*, 403.

AN EVALUATION OF MEDIA FOR DIAGNOSTIC CULTURES OF TUBERCLE BACILLI[1]

IRENE MELVIN, GEORGE C. KLEIN, WARREN JONES, AND MARTIN M. CUMMINGS

(Received for publication September 16, 1950)

INTRODUCTION

For many years investigators have searched for an ideal culture medium which would facilitate the isolation of tubercle bacilli from pathologic material. The ideal culture medium should have the following characteristics: It should support rapid growth of small numbers of tubercle bacilli. The colony morphology should be such as to permit easy differentiation between pathogenic and nonpathogenic acid-fast bacilli. The medium should inhibit the growth of contaminating microorganisms. The medium should be simple to prepare from readily available ingredients.

The literature contains many reports of culture media devised for primary isolation of tubercle bacilli (1–10). With few exceptions these media contain eggs, potatoes, and glycerin as their basic ingredients.

Since there are conflicting reports as to the diagnostic value of the many culture media described, since many of the studies employed laboratory strains of tubercle bacilli for evaluation of the growth-supporting ability of the media, and since some of the studies employed only small numbers of pathological specimens for evaluation, it was believed that a more thorough investigation of this problem was necessary. After a preliminary screening of a wide variety of culture media, six commonly used culture media were selected for more thorough evaluation.

MATERIALS AND METHODS

Jensen and Holm's modification of the Löwenstein medium was used as the standard medium against which the other culture media were tested. Pathologic specimens were cultured under routine laboratory conditions, using the same technique of digestion and inoculation. Comparisons were made of the numbers of colonies which appeared on the surface of the slants; time of the first appearance of the colonies; numbers of contaminants which appeared; and the morphologic characteristics of the colonies on each medium.

Specimens: Specimens were obtained from three sources:

1) Freshly collected specimens from wards of the Lawson Veterans Administration Hospital
2) Specimens from the Georgia State Department of Health, which were usually two to three days old
3) Specimens from Battey Hospital, a state tuberculosis hospital, which were mailed from a distance of 100 miles and were usually three to four days old.

[1] From the Laboratory Services of the Communicable Disease Center, Public Health Service, Federal Security Agency, Atlanta, Georgia.

These three sources provided an opportunity to test the media under a wide range of favorable and unfavorable conditions.

Media: The culture media evaluated in this study are presented below.

1. LÖWENSTEIN (JENSEN AND HOLM) MEDIUM (1)

Salt Solution:	1 flask
Monopotassium phosphate	2.4 gm.
Magnesium sulfate	0.24 gm.
Magnesium citrate	0.6 gm.
Asparagine	3.6 gm.
Glycerol	12 ml.
Distilled water	600 ml.
Potato flour	30 gm.
Homogenized whole eggs	1,000 ml.
Malachite green, 2 per cent aqueous solution	20 ml.

2. AMERICAN TRUDEAU SOCIETY EGG-YOLK-POTATO MEDIUM I (2)

Egg yolk	300 ml.
Potato water (8 per cent glycerin)	300 ml.

3. AMERICAN TRUDEAU SOCIETY EGG-YOLK-POTATO MEDIUM II (3)

Egg yolk	500 ml.
Potato flour water (2 per cent glycerol)	500 ml.

4. PETRAGNANI (McNABB) MEDIUM (4)

Milk	900 ml.
Potato flour	36 gm.
Peptone	6 gm.
Pieces of potato (size of an egg)	6
Eggs	24
Egg yolks	6
Glycerin	72 ml.
Aqueous malachite green solution, 2 per cent	60 ml.

5. PETRAGNANI (FROBISHER) MEDIUM (5)

Mixture A:	Milk	225.0 ml.
	Potato starch	9.0 gm.
	Peptone	1.5 gm.
	Diced potato	150.0 gm.
Mixture B:	Eggs	8.0
	Glycerin	18.0 ml.
	2 per cent aqueous malachite green	15.0 ml.
Mixture C:	Dextrose	1.5 gm.
	Asparagine	1.5 gm.
	Water	50.0 ml.

6. DUBOS OLEIC ACID-ALBUMIN-AGAR WITH PENICILLIN (*100 units per ml.*) (6)

Basal medium:	
KH_2PO_4	1.0 gm.
$Na_2HPO_4 \cdot 12H_2O$	6.0 gm.
Asparagine	1.0 gm.
Add:	
Casein	2 gm. (40 ml. of 5 per cent solution)
Ferric ammonium citrate	0.05 gm. (1 ml. of 1 per cent solution)
$CaCl_2$	0.005 gm. (1 ml. of 0.05 per cent solution)
$ZnSO_4$	0.0001 gm. (1 ml. of 0.01 per cent solution)

$CuSO_4$..... 0.0001 gm. (1 ml. of 0.01 per cent solution)

Made to 1-liter volume with distilled water.
Adjust pH to 6.5 with concentration HCl

Add:

1.5 per cent agar and autoclave (15 gm. per liter)
Cool to 50° C. and add oleic acid-albumin mixture and 100 units of penicillin per ml. aseptically.

Oleic acid-albumin mixture:

Dissolve 0.12 cc. oleic acid (0.1 gm.) in 10 ml. of N/20 NaOH
Add 5 ml. of this mixture to 95 cc. neutral 5 per cent fraction V albumin 0.85 per cent saline.
Sterilize by filtration.

The media were prepared following the directions given with the formulas as closely as possible. A total of 7,362 sputum specimens was employed in the study. Not all specimens were tested on all media.

Techniques: Each specimen was poured into a sterile Petri dish and the sputum was divided by means of sterile wooden applicators. A sample of each section of sputum (4 to 5 ml.) was placed in a centrifuge tube to be processed for culture as follows:

To the centrifuge tube containing the specimen was added an equal volume of 4 per cent NaOH, containing 0.004 per cent phenol red as an indicator. The tube was shaken vigorously for fifteen minutes. Following this, the specimen was centrifuged for fifteen minutes at 3,000 r.p.m. The supernatant fluid was poured off and to the sediment were added a few drops of 2N HCl for neutralization. Approximately 1 ml. of sediment then was inoculated onto four slants of medium with a Pasteur pipette. The same inoculum (approximately 0.25 ml. of the homogenized specimen) was made on two tubes of modified Löwenstein medium and two tubes of each of the other media tested. The cultures were incubated at 37° C. and were examined at the end of two weeks and every week thereafter for six weeks. A hand lens was used to examine the cultures.

All cultures were confirmed by Ziehl-Neelsen staining of the colonies. All atypical cultures were subcultured and inoculated into animals to confirm their virulence. The actual numbers of colonies which appeared on each culture tube were counted, unless the tubes were overgrown completely.

RESULTS

Since not all specimens were tested on all media, it has been necessary to tabulate the results obtained with each medium separately.

Comparison of Löwenstein-Jensen and American Trudeau Society medium I: Table 1 reveals that, of 1,309 specimens, 109 were positive for *M. tuberculosis* on Löwenstein-Jensen medium and were negative on the American Trudeau Society medium, whereas only 6 specimens were positive on the American Trudeau Society medium and negative on Löwenstein-Jensen medium. Ninety-eight and six-tenths per cent of all positive cultures were obtained on the Löwenstein-Jensen medium as compared to 75.5 per cent on the American Trudeau Society medium. This is a significant difference.[2]

[2] Formula for statistical analysis suggested by C. Richard Smith, M.D., Barlow Sanatorium, Los Angeles, California:

$$t = \frac{P_1 - P_2}{\sigma P_1 - P_2}$$

$t = 8.55$
$p = >0.000003$

Moreover, it may be seen that the average colony count per specimen on Lōwenstein-Jensen medium was 203.5 as compared to 143.4 on the American Trudeau Society medium. The average time of the first appearance of colonies on the Lōwenstein-Jensen medium was 20.5 days as compared to 22.0 days on the American Trudeau Society medium. Of greater significance, however, is

TABLE 1

Comparison of Lōwenstein-Jensen Medium and American Trudeau Society Medium I

A. *General Analysis of Specimens*

Total number of specimens	1,309
Total number of positives	445
Total number of negatives	842
Total number of contaminated	22

B. *Comparison of Amount of Growth on Different Media*

	Number	*Per Cent*
Positive L-J, positive ATS	330	74.2
Positive L-J, negative ATS	109	24.5
Negative L-J, positive ATS	6	1.3
Total positive L-J	439	98.6
Total positive ATS	336	75.5
Average number of colonies per specimen L-J	203.5	
Average number of colonies per specimen ATS	143.4	

C. *Comparison of Speed of Growth*

Average number of days first appeared L-J	20.5
Average number of days first appeared ATS	22.0

Time of First Appearance (in days)	*Lōwenstein-Jensen*		*American Trudeau Society Medium I*	
	Number	*Per Cent*	*Number*	*Per Cent*
7–14	27	6.2	10	3.0
15–21	331	75.4	203	60.4
22–28	53	12.1	102	30.4
29–35	18	4.1	14	4.2
36–42	7	1.6	5	1.5
>42	3	0.7	2	0.6

D. *Comparison of Contamination*

	Number	*Per Cent*
Total number of tubes each medium	2,618	
Number of tubes contaminated L-J	120	4.5
Number of tubes contaminated ATS	101	3.4

the fact that 81.6 per cent of the cultures were positive on Lōwenstein-Jensen during the first three weeks of incubation as compared to 63.4 per cent which were positive on the American Trudeau Society medium during this time.

There were more contaminated tubes (4.5 per cent) on Lōwenstein-Jensen medium than there were on the American Trudeau Society medium (3.4 per cent). The difference is barely significant.

Comparison of Löwenstein-Jensen medium and American Trudeau Society medium II: As may be seen in table 2, of 1,798 specimens, 37 (6.7 per cent) were positive on Löwenstein-Jensen medium and negative on American Trudeau Society medium II, whereas only 15 (2.7 per cent) specimens were positive on the

TABLE 2

Comparison of Löwenstein-Jensen Medium and American Trudeau Society Medium II

A. *General Analysis of Specimens*

Total number of specimens	1,798
Total number of positives	555
Total number of negatives	1,243

B. *Comparison of Amount of Growth on Different Media*

	Number	Per Cent
Positive L-J, positive ATS	503	90.6
Positive L-J, negative ATS	37	6.7
Negative L-J, positive ATS	15	2.7
Total positive L-J	540	97.3
Total positive ATS	518	93.3
Average number of colonies per specimen L-J	159.8	
Average number of colonies per specimen ATS	133.6	

C. *Comparison of Speed of Growth*

Average number of days first appeared L-J	21.4
Average number of days first appeared ATS	22.0

Time of First Appearance (in days)	Löwenstein-Jensen		American Trudeau Society Medium II	
	Number	Per Cent	Number	Per Cent
7–14	31	5.7	28	5.4
15–21	343	63.5	320	61.8
22–28	119	22.0	111	21.4
29–35	33	6.1	38	7.3
36–42	10	1.9	15	2.9
>42	4	0.7	6	1.2

D. *Comparison of Contamination*

	Number	Per Cent
Total number of tubes	3,640	
Number of tubes contaminated L-J	202	5.5
Number of tubes contaminated ATS	140	3.8

American Trudeau Society medium and negative on Löwenstein-Jensen medium. The Löwenstein-Jensen medium detected 97.3 per cent of the total positives as compared to 93.3 per cent of the total positives which were detected by the American Trudeau Society medium. The difference between these two values is not significant.[1]

[1] t = 3.1
p = 0.001

The average numbers of colonies of *M. tuberculosis* per specimen were 159.8 on Löwenstein-Jensen medium and 133.6 on the American Trudeau Society medium. This is a significant difference.

There was no significant difference between the average numbers of days required for first appearance of the colonies on the two media. Contamination was greater on the Löwenstein-Jensen (5.5 per cent) than on the American Trudeau Society medium (3.8 per cent).

TABLE 3

Comparison of Löwenstein-Jensen Medium and Petragnani (McNabb) Medium

A. *General Analysis of Specimens*

Total number of specimens	1,885
Total number of positives	585
Total number of negatives	1,273
Total number of contaminated	27

B. *Comparison of Amount of Growth on Different Media*

	Number	Per Cent
Positive L-J, positive McNabb	511	87.4
Positive L-J, negative McNabb	53	9.0
Negative L-J, positive McNabb	21	3.6
Total positive L-J	564	96.4
Total positive McNabb	532	90.9
Average number of colonies per specimen L-J	142.8	
Average number of colonies per specimen McN	100.3	

C. *Comparison of Speed of Growth*

Average number of days first appeared L-J	21.2
Average number of days first appeared McN	21.1

Time of First Appearance (in days)	Löwenstein-Jensen Number	Löwenstein-Jensen Per Cent	Petragnani (McNabb) Number	Petragnani (McNabb) Per Cent
7–14	22	3.9	17	3.2
15–21	380	67.3	378	71.4
22–28	123	21.8	107	20.1
29–35	26	4.0	19	3.3
36–42	13	2.0	11	2.0
>42	0	0.0	0	0.0

D. *Comparison of Contamination*

	Number	Per Cent
Total number of tubes	3,770	
Number of tubes contaminated L-J	137	3.4
Number of tubes contaminated P-McN	114	3.0

Comparison of Löwenstein-Jensen and Petragnani (McNabb) media: In table 3 it may be seen that, of 1,885 specimens, 53 were positive for *M. tuberculosis* on Löwenstein-Jensen medium and negative on the Petragnani-McNabb medium whereas only 21 specimens were positive on the Petragnani-McNabb medium

and negative on the Löwenstein-Jensen medium. Of the total positive specimens, 96.4 per cent were obtained on Löwenstein-Jensen medium as compared with 90.9 per cent on Petragnani-McNabb medium. The difference has been found to be of significance.[4]

TABLE 4

Comparison of Löwenstein-Jensen Medium and Petragnani (Frobisher) Medium

A. *General Analysis of Specimens*

Total number of specimens	1,055
Total number of positives	313
Total number of negatives	702

B. *Comparison of Amount of Growth on Different Media*

	Number	Per Cent
Positive L-J, positive Frobisher	272	86.9
Positive L-J, negative Frobisher	25	8.0
Negative L-J, positive Frobisher	16	5.1
Total positive L-J	297	94.9
Total positive Frobisher	288	92.0
Average number of colonies per specimen L-J	207.7	
Average number of colonies per specimen P-F	187.1	

C. *Comparison of Speed of Growth*

Average number of days first appeared L-J	21.4
Average number of days first appeared P-F	21.1

Time of First Appearance (in days)	Löwenstein-Jensen Number	Löwenstein-Jensen Per Cent	Petragnani (Frobisher) Number	Petragnani (Frobisher) Per Cent
7–14	0	0	0	0
15–21	210	70.8	203	70.5
22–28	71	23.9	73	25.3
29–35	12	4.0	8	2.8
36–42	4	1.3	4	1.4
>42	0	0	0	0

D. *Comparison of Contamination*

	Number	Per Cent
Total number of tubes	2,110	
Number of tubes contaminated L-J	277	13.1
Number of tubes contaminated P-F	191	9.0

The average number of colonies per specimen was 142.8 on Löwenstein-Jensen medium as compared with 100.3 on Petragnani-McNabb. There was no significant difference between the average numbers of days required for first appearance of the colonies. There was also no significant difference between the incidence of contamination of the two media.

[4] $t = 3.9$
$p = 0.00005$

Comparison of Löwenstein-Jensen and Petragnani (Frobisher) media: In table 4 it may be seen that 25, or 8 per cent, of the specimens were positive for *M. tuberculosis* on Löwenstein-Jensen medium and were negative on the Petragnani-Frobisher medium. These results are to be compared with 16 specimens (5.1 per cent) which were positive on Petragnani-Frobisher medium and negative on

TABLE 5

Comparison of Löwenstein-Jensen Medium and Dubos Oleic Acid-Albumin-Agar Medium
(100 Units Penicillin per Ml.)

A. *General Analysis of Specimens*

Total number of specimens	1,293
Total number of positives	199
Total number of negatives	1,054
Total number of contaminated	37

B. *Comparison of Amount of Growth on Different Media*

	Number	Per Cent
Positive L-J, positive Dubos	170	85.4
Positive L-J, negative Dubos	20	10.1
Negative L-J, positive Dubos	9	4.5
Total positive L-J	190	95.5
Total positive Dubos	179	89.9
Average number of colonies per specimen L-J	177.1	
Average number of colonies per specimen D	157.4	

C. *Comparison of Speed of Growth*

Average number of days first appeared L-J	23.1
Average number of days first appeared D	23.4

Time of First Appearance (in days)	Löwenstein-Jensen		Dubos Oleic Acid-Albumin-Agar	
	Number	Per cent	Number	Per Cent
7–14	4	2.1	2	1.1
15–21	103	54.2	89	50.0
22–28	64	33.7	67	37.2
29–35	13	6.8	16	8.9
36–42	2	1.1	3	1.7
>42	4	2.1	2	1.1

D. *Comparison of Contamination*

	Number	Per Cent
Total number of tubes	2,586	
Total number of tubes contaminated L-J	231	9.0
Total number of tubes contaminated D	101	4.6

Löwenstein-Jensen medium. Ninety-four and nine-tenths per cent of the total positive cultures were obtained on Löwenstein-Jensen medium compared with 92 per cent positives obtained on Petragnani-Frobisher. These differences are not significant.[8]

[8] $t = 1.5$
$p = 0.067$

The average number of colonies per specimen was 207.7 on the Löwenstein-Jensen medium compared with 187.1 on Petragnani-Frobisher medium. There was no significant difference in the number of days required for first appearance of colonies. There was a greater number of contaminated tubes with Löwenstein-Jensen medium (13.1 per cent) than with Petragnani-Frobisher medium (9 per cent).

Comparison of Löwenstein-Jensen and oleic acid-albumin-penicillin-agar media: As shown in table 5, of 1,293 specimens, 20 were positive on Löwenstein-Jensen medium and were negative on oleic acid-albumin-agar medium; whereas only 9 were positive on the oleic acid-albumin-agar medium and were negative on Löwenstein-Jensen medium. Ninety-five and five-tenths per cent of the total positives were obtained on Löwenstein-Jensen medium as compared with 89.9 per cent positives on oleic acid-albumin-agar medium. This is not a very significant difference.[6] It may also be seen that there were greater numbers of colonies per specimen obtained on the Löwenstein-Jensen medium than on the oleic acid-albumin-agar medium. There was no significant difference in the time of first appearance of colonies on the two media. There was a greater number of contaminated tubes (9.0 per cent) on Löwenstein-Jensen medium than was obtained on the oleic acid-albumin-agar medium (4.6 per cent).

DISCUSSION

The present study was performed under routine laboratory conditions and the comparisons of the media should be interpreted in this light. This explains the varying distribution of positive specimens and it also explains the variations in amount of contamination throughout the study. In general, contamination was more frequent during the summer than during the remainder of the year.

Although not included in the data reported in this study, it should be pointed out that approximately 1,500 gastric washings and other body fluids were also examined during this two-year period. The cultural results obtained on the different media were essentially the same as those observed with the sputum specimens.

In the present study there were certain observations which do not lend themselves to tabulation but merit discussion. A considerable difference was noted in colonial morphology on the culture media tested. A large number of colonies on the tubes of both American Trudeau Society media tended to be moist and creamy, and often required animal inoculation to determine whether or not they were tubercle bacilli or acid-fast saprophytes. Colonies of tubercle bacilli on two modifications of Petragnani and on Löwenstein-Jensen medium were usually dry, rough, and friable, and for the most part were easy to differentiate from acid-fast saprophytes. It was rather difficult to identify tubercle bacilli on the oleic acid-albumin medium on the basis of colonial morphology since occasionally acid-fast saprophytes produced rough colonies with serpentine cords and more frequently tubercle bacilli grew as smooth dewdrop-like colonies. All atypical colonies were injected into guinea pigs to determine virulence.

[6] $t = 2.16$
$p = 0.014$

It is reasonably certain that all of the positive cultures reported in this study represent human-type tubercle bacilli.

The most striking observation throughout the entire study was the finding of greater numbers of colonies on Löwenstein-Jensen medium than on any of the other media tested. Only Frobisher's modification of Petragnani medium approached the Löwenstein-Jensen medium in this respect. On the other hand, it appeared that contamination was seen more frequently on Löwenstein-Jensen medium than on the other media tested.

It should be pointed out that approximately 15 to 20 per cent of the specimens employed in the study were negative for acid-fast bacilli by microscopic examination of stained smears. In the evaluation of any diagnostic culture medium, it is important that the pathologic material used contain few, as well as many, tubercle bacilli, for the sensitivities of the various media appear to be uniform when heavy plantings of tubercle bacilli are used. Finally, it also should be mentioned that the media which gave the best results are much more complex and, therefore, are more difficult to prepare. Nevertheless, their increased efficiency certainly would justify their use.

SUMMARY

In a comparative test, using objective, quantitative evaluation of five diagnostic culture media for tubercle bacilli, the Jensen-Holm modification of the Löwenstein medium was found to have more favorable attributes for the isolation of *M. tuberculosis* from human sources than the other media tested. Several of the differences in numerical results were of only borderline significance. The American Trudeau Society medium, containing 2 per cent glycerol, was superior to the medium containing 8 per cent glycerol.

SUMARIO

Justipreciación de los Medios para el Cultivo Diagnóstico de los Bacilos Tuberculosos. Estudio Basado en 7,362 Ejemplares de Esputo

En una prueba comparativa, empleando una valuación cuantitativa, objetiva de los medios de cultivo para diagnóstico de los bacilos tuberculosos, la modificación Jensen-Holm del medio de Löwenstein mostró que poseía atributos más favorables que los otros medios comprobados. Varias de las diferencias en los resultados numéricos no revestían importancia bien deslindada. El medio de la Sociedad Americana Trudeau, que contiene 2 por ciento de glicerol, es superior al de la Comisión Trudeau, que contiene 8 por ciento de glicerol.

RESUME

Une évaluation des milieux de culture pour l'identification du bacille tuberculeux. Etude fondée sur 7.362 spécimens de crachats

Dans un test comparatif pour la détermination objective et quantitative des milieux de culture pour l'identification du bacille tuberculeux, on a trouvé que le milieu Jensen-Holm, qui est une modification du milieu Löwenstein, avait des

propriétés plus satisfaisantes que les autres milieux expérimentés. Plusieurs des différences notées dans les résultats numériques n'avaient qu'une importance limitée. Le milieu "American Trudeau Society", contenant 2 par cent de glycérine est supérieur au milieu "Trudeau Committee" qui contient 8 par cent de glycérine.

REFERENCES

(1) Holm, J., and Lester, V.: Diagnostic demonstration of tubercle bacilli, Acta tuberc. Scandinav., 1941, *16*, 3.

(2) American Trudeau Society: Report of the Committee on Evaluation of Laboratory Procedures, Am. Rev. Tuberc., 1946, *54*, 428.

(3) American Trudeau Society: Report of the Committee on Evaluation of Laboratory Procedures, 1949, personal communication.

(4) McNabb, A. L.: Cultural methods of isolation of tubercle bacilli, Am. J. Pub. Health, 1936, *26*, 619.

(5) Frobisher, M. M., Jr.: Fundamentals of Bacteriology, W. B. Saunders and Company, Philadelphia and London, 1940, p. 658.

(6) Dubos, R. J., and Middlebrook, G.: Media for tubercle bacilli, Am. Rev. Tuberc., 1947, *56*, 334.

(7) Corper, H. J., and Cohn, M. L.: Media for tubercle bacilli: An evaluation of different media for diagnostic cultures of tubercle bacilli, Am. Rev. Tuberc., 1942, *48*, 560.

(8) Schwabacher, H.: A comparison of different media for the growth of the tubercle bacillus, Tubercle, 1937, *18*, 199.

(9) Cerutti, F. C.: The culture of *B. tuberculosis* on Petragnani's medium, J. Trop. Med., 1932, *35*, 157.

(10) Sasano, K. T., and Medlar, E. M.: Egg-yolk-potato medium: Its efficacy for demonstrating small numbers of tubercle bacilli, Am. Rev. Tuberc., 1943, *48*, 297.

CLINICAL COMPARISON OF SEVERAL CULTURE MEDIA IN THE DIAGNOSTIC DEMONSTRATION OF TUBERCLE BACILLI[1, 2]

C. RICHARD SMITH

(Received for publication October 17, 1950)

INTRODUCTION

Based on the studies of Sasano and Medlar (1), a culture medium containing approximately 50 per cent egg yolk, 12 per cent potato (or 2 per cent potato starch), 4 per cent glycerol, and 0.02 per cent malachite green was recommended for the diagnostic demonstration of tubercle bacilli by the Committee on the Evaluation of Laboratory Procedures of the American Trudeau Society in 1946 (2). In another study (3), variations of this formula were superior to Petragnani medium in supporting the growth of tubercle bacilli. Experimentally, it was found that fresh potato and potato flour (starch) were about equal in growth-supporting ability; and that glycerol concentrations of 5 per cent or more were inhibitory, whereas levels of 1 to 3 per cent were sufficient for optimum growth. Subsequent experimental comparisons (4) indicated superiority for the buffered whole egg-potato flour medium of Löwenstein as modified by Jensen (5) over any of the above formulas.

For the past three years a study has been conducted in which clinical material has been planted simultaneously on media of various formulas so as to compare their worth in actual practice. The results of this study constitute the basis of the present report.

MATERIALS AND METHODS

Sputum, stomach contents, or the two combined were obtained from in- and out-patients of the Sanatorium and from referred diagnostic cases. All specimens were first shaken with sodium hydroxide by machine for seven minutes. Centrifuging was at 2,000 r.p.m. for seven minutes. The exposure of specimens to decontaminators was made at room temperature and the period was generally between twenty and thirty minutes. After processing, each sediment was mixed and planted two drops to a tube. The order of seeding the different media was varied.

Standard formulas were modified so that each medium contained 0.03 per cent malachite green. The egg-yolk-potato formulas will be referred to as ATS (American Trudeau Society) media. The media were put up in 6 by ½ inch tubes, closed with cotton, and inspissated at 86°C. for forty minutes, as recommended by Cummings (6). Final closure after planting was with rubber stoppers. Readings were made at two, three, four, five, six, and eight weeks. The characteristics of color, roughness, coherency, and friability of colonies were noted. Consistency and acid-fastness of all growths were tested. Atypical growths were inoculated into guinea pigs to determine their virulence.

RESULTS

Löwenstein and ATS formulas A and B: In a three-way comparison (table 1) the buffered whole egg-potato flour (Löwenstein-Jensen) formula yielded tuber-

[1] From the Laboratory of the Barlow Sanatorium, Los Angeles, California.

[2] This study was made possible, in part, by a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, medical section of the National Tuberculosis Association.

cle bacillus growth from more specimens than did either of the ATS formulas. The superiority of Löwenstein medium over the ATS-A (fresh potato, 3 per cent

TABLE 1

Comparison of the Löwenstein and American Trudeau Society Formulas A† and B‡ Gastric Contents with or without Added Sputum§ Cultured on Two Tubes of Each Medium*

	TOTAL		LÖWENSTEIN*		ATS-A†		ATS-B‡	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total specimens	1,999	100	1,999	100	1,999	100	1,999	100
Positive for *M. tuberculosis*	425	21.2	338	16.9	286	14.3	298	14.9
Growth appearing within 3 weeks			91	27.0‖	107	37.6‖	98	32.9‖
"Typical" growths			287	84.9‖	137	47.9‖	161	54.0‖
Tests contaminated¶			28	1.4	37	1.8	44	2.2
Tubes contaminated	529	4.4**	117	2.0**	179	4.5**	233	5.8**

* Whole eggs, 60 per cent (vol.); potato flour, 1.8 per cent; glycerol, 0.7 per cent (vol.); asparagine, 0.22 per cent; KH_2PO_4, 0.145 per cent; $MgSO_4$, 0.015 per cent; magnesium citrate, 0.036 per cent; malachite green, 0.03 per cent.

† Egg yolk, 50 per cent (vol.); fresh potato, 10 per cent; glycerol, 3 per cent (vol.); malachite green, 0.03 per cent.

‡ Egg yolk, 50 per cent (vol.); potato flour, 2 per cent; glycerol, 1 per cent (vol.); malachite green, 0.03 per cent.

§ Each specimen shaken with one-tenth of its volume of 7.5 per cent sodium hydroxide.

‖ Per cent of positive specimens for that culture medium.

¶ Sufficiently to prevent growth of tubercle bacilli.

** Per cent of total tubes of that medium inoculated.

TABLE 2

A Comparison of the Löwenstein and American Trudeau Society Formulas B and C Sputum† Cultured on Two Tubes of Each Medium*

	TOTAL		LÖWENSTEIN		ATS-B		ATS-C*	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total specimens	546	100	546	100	546	100	546	100
Positive for *M. tuberculosis*	166	30.4	152	27.9	131	24.0	130	23.8
Growth appearing within 3 weeks			58	38.2	47	35.9	54	41.5
"Typical" growths			110	72.4	74	56.5	63	48.5
Tubes contaminated			33	3.0	53	4.8	54	4.9

* Egg yolk, 50 per cent (vol.); fresh potato, 20 per cent; glycerol, 2 per cent (vol.).

† Shaken with an equal amount of 0.5 per cent sodium hydroxide and this mixture further treated with an equal amount of 2.5 per cent oxalic acid.

glycerol) formula is significant; that over the ATS-B formula (potato flour, 1 per cent glycerol) is not quite significant ($P < 0.1$). The slight superiority of ATS-B over the A formula is not significant. On the other hand (line 3 of table 1), the ATS-A formula supported the highest number of early (in the first three weeks)

growths and the Löwenstein formula the lowest number of such growths. The ATS-B allowed most contaminants; the Löwenstein medium, the least.

Being aware of the considerable subjective error and personal variation in recording the character of colonial growth, an attempt was made to obtain a value which roughly would express the results of these observations. "Typical"

TABLE 3

A Comparison of the Löwenstein and American Trudeau Society Formulas B and C Gastric Contents Pooled with Sputum and Cultured on Four Tubes of Each Medium*

	TOTAL		LÖWENSTEIN		ATS-B		ATS-C	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total specimens	541	100	541	100	541	100	541	100
Positive for *M. tuberculosis*	120	22.2	101	18.7	90	16.6	87	16.1
Growth appearing within three weeks			30	29.7	34	37.8	36	41.4
"Typical" growths			78	77.2	50	55.6	38	43.7
Tubes contaminated			120	5.5	136	6.3	171	7.9

* Pooled specimens were shaken with one-eighth of their volume of 4 per cent sodium hydroxide. Half of the mixture was further treated with an equal amount of 2.5 per cent oxalic acid. Sediments from both halves were planted on two tubes of each medium.

TABLE 4

A Comparison of the Löwenstein and Corper Formulas*

Specimens of Sputum† and of Gastric Contents with or without Added Sputum‡ Cultured on One Tube Each of Each Medium

	TOTAL		LÖWENSTEIN		CORPER	
	Number	Per cent	Number	Per cent	Number	Per cent
Total specimens	1,223	100	1,223	100	1,223	100
Positive for *M. tuberculosis*	173	14.1	129	10.5	126	10.3
Growth appearing within 3 weeks			47	36.4	48	38.1
"Typical" growths			111	88.8	91	72.2
Tubes contaminated			58	4.7	146	11.1

* Egg yolk, 72 per cent (vol.); glycerol, 3 per cent (vol.); malachite green, 0.03 per cent.

† Sputum shaken with an equal amount of 1.5 per cent sodium hydroxide.

‡ Gastric-sputum specimens shaken with one-tenth of their volume of 7.5 per cent sodium hydroxide.

applies only to those growths showing the characteristics considered useful in distinguishing tubercle bacilli from other microorganisms, particularly non-pathogenic acid-fast bacilli. These include color, roughness, firmness, and friability. As shown in line 4 of table 1, the superiority of the Löwenstein formula in this respect is outstanding. This finding coincides with the general impression held by all of the technicians in this laboratory.

The Löwenstein and ATS formulas B and C: Because of the tendency for the

ATS media, particularly A, to be wet and to yield growths of "atypical" smoothness or softness, the amount of potato in the A formula was increased from 10 to 20 per cent. Tables 2 and 3 show the results of comparisons of this ATS-C formula with the ATS-B and Löwenstein media. The results for cultures of sputum (table 2) and of gastric contents, with or without added sputum (table 3), are given separately because the pretreatment and the numbers of tubes per specimen were different. In each group Löwenstein medium yielded tubercle bacillus growth the most often, although its superiority was not quite significant. There was no significant difference between ATS formulas B and C. ATS media B and C supported more early growths than the Löwenstein medium in the gastric contents group (table 3) but not in the sputum group (table 2).

In both groups the Löwenstein formula produced more "typical" growths and fewer contaminations. The increased potato content of the ATS-C formula did not seem to have notably improved the character of the colonial growth.

Löwenstein and Corper media: Table 4 shows a nonsignificant superiority for the Löwenstein over the Corper formula in the yield of positive results even though the latter was subject to three times as much contamination. The earliness of positive growths is approximately the same for each medium and the Löwenstein formula shows less advantage in the production of "typical" colonies than in the other comparisons. While the colonies on the Corper medium were usually firm and friable, they tended to be smooth and flat.

DISCUSSION

The comparison of different culture medium formulas for the clinical demonstration of tubercle bacilli is precarious. The complex organic components, egg and potato, are subject to considerable variation according to region, season of the year, freshness, and final processing. A favorite medium unintentionally may receive more favorable handling. The final test is in actual clinical usage, and here large series must be run to overcome chance distribution.

The buffered egg-potato medium of Löwenstein as modified by Jensen was superior in all respects, except earliness of growth, and in every comparison. While the differences in most cases were not significant, the constancy of its superiority is impressive. The egg yolk medium of Corper most closely approached the Löwenstein formula and except for a disadvantage in the production of "typical" colonies might be considered of equal worth. The proportion of earlier growth produced by the ATS formulas does not seem sufficiently greater or consistent enough to outweigh the disadvantages of these media.

The invariable production of more "typical" colonies by the Löwenstein medium than by the other formulas is an important consideration. In our experience "atypical" colonies of tubercle bacilli may frequently approach the appearance and soft consistency of the buff-colored acid-fast saprophytes and, conversely, the occasional buff-colored saprophyte colonies may be almost indistinguishable from those of virulent acid-fast bacilli. This creates the opportunity for false diagnoses either in a positive or negative direction and makes necessary more frequent virulence tests.

SUMMARY

For the isolation of *M. tuberculosis* from human sources the buffered egg-potato medium of Löwenstein as modified by Jensen proved as good and probably better than three variations of the ATS egg-yolk-potato formula and the Corper egg yolk medium.

The Löwenstein formula was superior in the yield of positive results and in the production of "typical" growths which are more easily identified.

The Corper egg yolk medium was about as good as the Löwenstein except in production of "typical" growths.

Of the variations of the American Trudeau Society media, formula B containing potato flour and 1 per cent glycerol appeared to be the best although its superiority was not statistically significant.

SUMARIO

Comparación Clínica de Varios Medios de Cultivo en el Descubrimiento Diagnóstico de Bacilos Tuberculosos

En pruebas clínicas, el medio regulado de patata-huevo de Löwenstein, según lo modificara Jensen, resultó tan bueno como, y probablemente mejor que, tres variaciones de la fórmula de patata-yema de huevo de la Sociedad Americana Trudeau y que el medio de yema de huevo de Corper, para el aislamiento de bacilos tuberculosos.

La fórmula de Löwenstein resultó superior en rendimientos positivos y en la producción de colonias "típicas," que es más fácil identificar.

El medio de yema de huevo de Corper resultó más o menos tan bueno como el de Löwenstein, salvo en producción de colonias "típicas."

De las variaciones de la Sociedad Americana Trudeau, la fórmula B, que contiene harina de patata y 1 por ciento de glicerol, pareció ser la mejor, aunque su superioridad no fué estadísticamente significativa.

RESUME

Comparaison de différents milieux de culture pour l'identification du bacille tuberculeux

L'essai en clinique du milieu tamponné oeuf-pomme de terre de Löwenstein, tel qu'il a été modifié par Jensen, s'est montré aussi bon et probablement meilleur pour isoler le bacille tuberculeux que les trois variétés de la formule jaune d'oeuf-pomme de terre de l'American Trudeau Society et que le milieu au jaune d'oeuf de Corper.

La formule de Löwenstein s'est montrée supérieure dans la production de résultats positifs et de cultures "typiques" plus aisément identifiées.

Le milieu de Corper au jaune d'oeuf s'est montré aussi satisfaisant que le milieu de Löwenstein, sauf dans la production de cultures "typiques."

Parmi les milieux de l'American Trudeau Society, la formule B, qui contient de la farine de pomme de terre et 1 pour cent de glycérol, semble le meilleur, toutefois sa supériorité du point de vue statistique, n'est pas appréciable.

Acknowledgment

The author wishes to acknowledge help in statistical analysis of the material given by Mr. Frank Oechsli.

REFERENCES

(1) Sasano, K. T., and Medlar, E. M.: Egg-yolk-potato medium, Am. Rev. Tuberc., 1943, *48*, 297.

(2) American Trudeau Society: Report of the Committee on the Evaluation of Laboratory Procedures of the American Trudeau Society, Am. Rev. Tuberc., 1946, *54*, 438.

(3) Whitely, H. R., Hoyt, A., and Smith, C. R.: Report to the Committee on Evaluation of Laboratory Procedures of the American Trudeau Society, 1947.

(4) Smith, C. R., and Cannon, M.: Report to the Committee on Medical Research and Therapy of the American Trudeau Society, 1948.

(5) Holm, J., and Lester, V.: Diagnostic demonstration of tubercle bacilli, Acta tuberc. Scandinav., 1941, *16*, 310.

(6) Cummings, M. M.: Personal communication.

(7) Corper, H. J., and Cohn, M. L.: The nutrient quality of eggs for growing tubercle bacilli, Am. J. Hyg., 1933, *18*, 1.

Case Reports

ACUTE DISSEMINATED COCCIDIOIDAL GRANULOMA[1,2]

WILLIAM HENTEL, J. K. NEWTON, AND R. K. HORSMAN

(Received for publication August 25, 1950)

CASE RECORD

Clinical course: The patient, a 32-year-old Negro male, entered the hospital on May 17, 1950, complaining of increasing tiredness and weight loss of thirty pounds since January 1950. In March 1950, he had developed a productive cough which had persisted. Fever and diarrhea began in April 1950. Despite treatment by his private physician, all of his symptoms progressed until the time of hospitalization. The patient's history included army service from May 21, 1941 to June 19, 1945, with thirty-two months' duty in the South Pacific area. On admission to this hospital, he appeared acutely ill and emaciated, with a temperature of 101°F., pulse 88, and respirations, 22 per minute. Blood pressure was 120 systolic, 80 diastolic in mm. of mercury. He weighed 116 pounds, which was approximately thirty pounds under his average weight. Physical examination of the chest revealed rales scattered throughout both lungs. The skin over the abdomen contained numerous pigmented, purplish, blotchy areas measuring up to 4 mm. in diameter. The patient stated that these skin lesions had been present for a long time. A moderate stiffness of the neck was reported by the first examiner but was not found by subsequent examiners. Roentgenographic studies on admission (figure 1) revealed a patchy infiltration throughout the right lung, extending from apex to base. The left lung showed similar infiltrations with pleural thickening in the region of the fissure. Laboratory studies were as follows: urine, normal; erythrocytes, 2.0 million per cu. mm.; total leukocyte count, 14,600 per cu. mm.; hemoglobin, 43 per cent; hematocrit, 20; erythrocyte sedimentation rate, 16 mm. (Wintrobe corrected); differential leukocyte percentage: polymorphonuclears, 80; Stab forms, 4; myelocytes, 5; lymphocytes, 11. Because of anemia, the patient was given four transfusions (1,500 cc.), after which, on June 29, 1950, the erythrocytes were 3.6 million per cu. mm., the hemoglobin, 79 per cent; and the hematocrit, 35 per cent. The patient's temperature continued to fluctuate daily to as high as 104°F. with a pulse rate as high as 120 to 125 per minute. He passed several watery stools daily. Diarrhea was relieved slightly with paregoric and bismuth medication. Two stool examinations were negative for occult blood, ova, and parasites, and cultures for pathogens were negative. Two 24-hour sputum concentrates were reported negative for tubercle bacilli (June 19 and 20, 1950). Cultures of sputum were negative for tubercle bacilli at date of death. Lumbar puncture performed June 19, 1950 revealed an essentially normal fluid. On that date the cerebrospinal fluid was clear, contained 5 cells per cu. mm., a sugar concentration of 68 mg. per 100 cc., and chlorides of 618 mg. per 100 cc. Culture of the specimen was sterile at date of death. The patient continued his febrile downhill course. On several occasions he was listless, confused, and complained of vague headaches. On June 27, 1950 he developed a vesicular type of abdominal rash which had not been noted previously. Two days later, small subcutaneous bluish nodules were noted over the chest, abdomen, and upper extremities. Blood for culture

[1] From Veterans Administration Hospital, Legion Branch, Kerrville, Texas.

[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

was taken and skin biopay requested, but the patient expired before the latter procedure could be carried out. He died on June 30, 1950.

The clinical diagnosis was: (*1*) acute, disseminated tuberculosis; (*2*) pulmonary tuberculosis, reinfection type.

Post-mortem findings: The body was that of a fairly well developed, poorly nourished Negro male, measuring 68 inches in length and weighing approximately 120 pounds. The external examination was essentially negative with the exception of bluish, subcutaneous nodules which measured up to 0.5 cm. in diameter, scattered over the abdominal, thoracic, and upper extremity surfaces. The nodules were firm, freely movable, and upon excision demonstrated central areas of thick, greenish pus. The combined weight of the lungs was

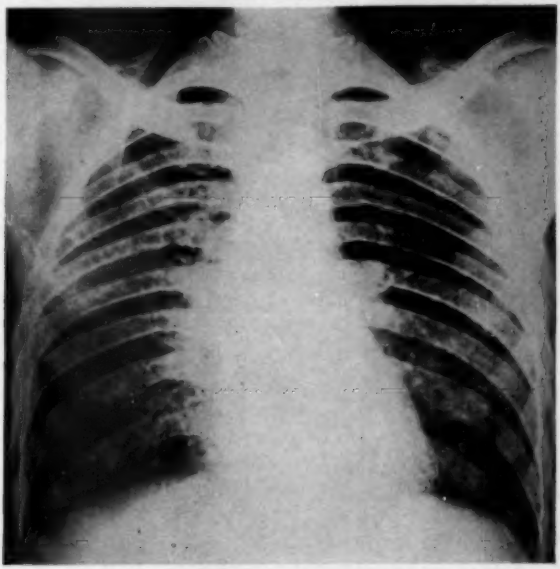


FIGURE 1. Roentgenogram of chest, May 18, 1950. Diffusely disseminated lesions throughout both lungs.

2,350 gm. Both lungs were crepitant but upon palpation gave a feeling of being studded with small, firm nodules. The cut surfaces were pink to gray with a fine dispersion of discrete and confluent, well-demarcated, millet-seed-sized, grayish nodules. No cavitation or caseation was seen. The right middle lobe on gross examination resembled gray pneumonic hepatization. The bronchial tree of the right lung was filled with thick, yellow pus. The left lung presented a similar picture. The hilar lymph nodes were slightly enlarged and studded with small, grayish, millet-seed-sized nodules. The bifurcation lymph nodes were completely caseated and the overlying trachea presented a small, posterior, red, mucosal ulceration measuring 0.4 cm. in diameter. The heart weighed 400 gm. On gross examination, the heart showed scattered, grayish, myocardial nodules measuring up to 0.5 cm. in diameter. Two similar nodules were seen in the subepicardial region. The spleen weighed 300 gm. The cut surfaces were mushy, but no nodular accumulations could be seen. The liver weighed 2,100 gm. and was firm and light tan in color. The cut surfaces demonstrated

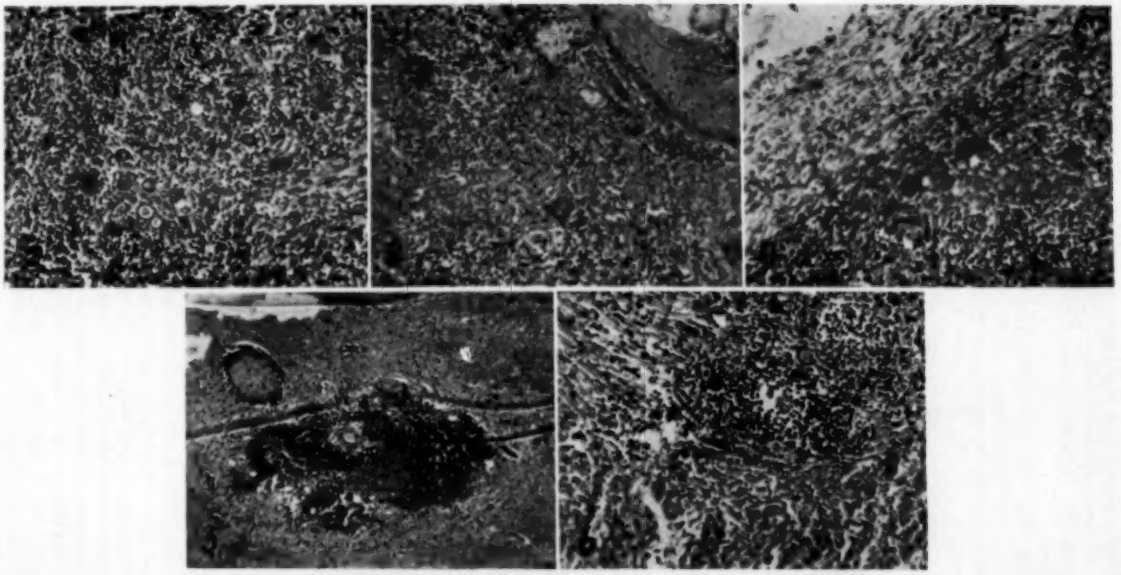


FIG. 2. Photomicrograph: lung section demonstrating coccidioidal granuloma. (×170)
FIG. 3. Photomicrograph: skin, coccidioidal endospores, surrounded by chronic granulomatous reaction. (×105)
FIG. 4. Photomicrograph: mesenteric lymph node with coccidioidal bodies. (×105)
FIG. 5. Photomicrograph: brain. Localized coccidioidal granuloma surrounding small capillary. (×90)
FIG. 6. Photomicrograph: heart. Myocardial granuloma with many coccidioidal bodies. (×60)

an occasional small, grayish nodule. The pancreas was normal in size, shape, and position. The intestines were grossly normal. The mesenteric lymph nodes were reddish and enlarged. The adrenals showed no abnormalities. The kidneys were of normal weight and the capsule stripped easily, revealing a smooth, congested cortex. The cut surfaces showed scattered, grayish, millet-seed-sized nodules throughout the entire parenchyma. There were no gross abnormalities in the skeletal system. The bone marrow was pale, but abundant in amount. The brain weighed 1,500 gm. and appeared normal externally. Sagittal sections through the cerebral and cerebellar hemispheres were not remarkable except for one small, poorly defined, grayish nodule, 0.1 cm., located in the subcortical region of the right frontal lobe.

Sections taken from skin nodules, lungs, pulmonary regional lymph nodes, heart, spleen, liver, mesenteric lymph nodes, kidneys, bone marrow, and brain all demonstrated coccidioidal granulomata (figures 2, 3, 4, 5, and 6).

Blood withdrawn on June 29, 1950 yielded a pure culture of *Coccidioides immitis*. Blood withdrawn from the heart for culture post mortem on June 31, 1950 yielded a growth of *Coccidioides immitis*.

Cerebrospinal fluid obtained post mortem showed no growth on culture.

COMMENT

An unusual case of coccidioidal dissemination is presented. This condition, although by no means rare, can still be classified as uncommon, and should be of interest to physicians, especially those specializing in pulmonary diseases. Unless one is alert, the condition may be diagnosed as disseminated tuberculosis, as occurred in the present case. The presence of scattered subcutaneous nodules or "abscesses" should arouse the suspicion that one is confronted by a disseminated fungal infection. This manifestation is reported to be more common in disseminated infections with *Blastomyces* or *Actinomyces*, but is known to occur in coccidioidal infection, usually following dissemination. In the rapidly progressive dissemination, death may occur before these subcutaneous abscesses have had time to break down and yield the draining sinuses that are more characteristic of fungal infections, as seen by clinicians generally (1, 2).

SUMMARY

The clinical and post-mortem findings in a case of disseminated coccidioidal granuloma are presented. The diagnosis was confirmed by isolation of *Coccidioides immitis* from blood withdrawn ante mortem.

REFERENCES

(1) Manual of Clinical Mycology, W. B. Saunders, Philadelphia, 1945, pp. 51–63.
(2) Bacterial and Mycotic Infections in Man, J. P. Lippincott, Philadelphia, 1948, pp. 616–619.

LÖFFLER'S SYNDROME[1,2]

Transient Pulmonary Infiltration with Eosinophilia

CHARLES A. HEIKEN AND E. ROBERT WIESE

(Received for publication April 26, 1950)

INTRODUCTION

In 1932 Löffler (1) described a condition which has since been known as Löffler's syndrome. In 1936 he published a second paper wherein he again described the signs and symptoms constituting the syndrome (2). Many cases have been reported and a large bibliography regarding the syndrome has accumulated since the appearance of the first article. As the scope of this paper does not permit the discussion of even the most important of these papers, the reader is referred to the excellent article by Pierce, Crutchlow, Henderson, and McKay (3) which also includes the report of eight cases and a comprehensive bibliography.

SYMPTOMATOLOGY

Löffler's syndrome is characterised by the marked discrepancy between the clinical signs and the striking—at times alarming—laboratory findings. The general health of the patient very often is not impaired. Many of the patients are unaware of their disease which is discovered either by accident, in mass roentgenographic surveys, or in persons suspected of having pulmonary tuberculosis. Symptoms, when present, are slight fatigue and lassitude; an irritating, scanty, mucopurulent sputum, which may contain eosinophils; and a normal or, at the most, a moderate elevation of temperature. Abnormal findings on examination of the chest are few or may even be absent. Slight dullness, increased intensity of normal breath sounds, a few rales, and occasionally some friction rubs may be found.

ROENTGENOGRAPHIC ABNORMALITIES AND EOSINOPHILIA

Roentgenograms of the chest show varying degrees of pulmonary involvement, ranging from small or round infiltrations to extensive, irregular shadows. These may be faint or dense, unilateral or bilateral; they may be flocculent or sharply defined in outline; and may be confined to one lobe or may involve the entire lung. The fleeting, migratory character of these infiltrations, however, is the essential and distinctive feature of these infiltrations. They appear in a relatively short time and disappear within a week to ten days only to reappear in other parts of the lung and again disappear in the same manner.

The roentgenographic findings in the chest are associated with a marked eosinophilia. While only a slight leukocytosis, ranging from 12,000 to 15,000 cells per cu. mm., is present, the eosinophilic percentage ranges from 10 to 30 and an eosinophilic percentage as high as 66 has been reported. The eosinophilia makes its appearance simultaneously with the roentgenographic abnormalities and therefore should not be looked upon as a postinfection phenomenon. The extent of the pulmonary involvement, however, cannot be estimated by the degree of the eosinophilia as no parallel between the two has ever

[1] From Mont Alto Sanatorium, South Mountain, Pennsylvania, and Women's Medical College, Philadelphia, Pennsylvania.

[2] Presented at the meeting of the Pennsylvania Tuberculosis and Health Society, held at the William Penn Hotel, Pittsburgh, Pennsylvania, May 26, 1949.

been demonstrated. The erythrocyte sedimentation rate usually ranges from 8 to 15 mm. in a one-hour period.

ETIOLOGY

In all likelihood there is probably no single etiologic factor for the production of this condition. Löffler believed the syndrome was brought about by an atypical form of tuberculosis. Nevertheless, 37.1 per cent of the cases presented by Löffler occurred in patients who were nonreactors to tuberculin, so that tuberculosis can scarcely be the causative factor. Today it is generally agreed that the syndrome is the allergic response to any one of many allergens. Engel (4) presented a persuasive paper in 1935, wherein he described the disease as an allergic reaction to the privet flower. Alfers (5) has recently presented a case which he believes represented a reaction to ragweed pollen. Although intestinal parasites produce a surprisingly high degree of eosinophilia and the pulmonary shadows may be regarded as the allergic response to the intestinal infection, it should be questioned seriously whether cases in which the larvae of the intestinal parasites have invaded the lungs should be classified as Löffler's syndrome.

Many European writers have mentioned the seasonal onset of the disease. Löffler, for example, detected the majority of his cases during July and August; the cases described by Engel all occurred in May. It is also interesting to note that males are affected twice as often as females; most of the cases have occurred in adults. The condition has also been reported in members of the same family.

PATHOLOGY

Löffler's syndrome is a benign disease and no fatal cases have been reported. Few cases, therefore, have come to autopsy. The four cases cited by von Meyenburg (6) are most often quoted. Three of these men died of gunshot wounds; the fourth died of traumatic tetanus in three days. All of these men had been in good health and pulmonary involvement had not been suspected. The macroscopic findings at postmortem differed little, if at all, from that of bronchopneumonia; microscopically the alveoli contained a true inflammatory exudate in which eosinophils predominated, and there was also marked eosinophilic parenchymal infiltration. Other organs, such as the liver and spleen, were also infiltrated with eosinophils. A high percentage of eosinophils was present in the peripheral blood in all cases.

INCIDENCE

Because so many of the cases occur in apparently healthy persons and because even the patients who do complain present such insignificant symptoms, it is not improbable that Löffler's syndrome is more common than is generally believed. More cases will likely be found since mass roentgenographic surveys of the chest are being done more or less routinely in many states. The trilogy of absence of symptoms, or of slight symptoms, the transient successive infiltrations of the chest, and the elevated percentage of blood eosinophils are the things to bear in mind constantly. It must be remembered that all lung shadows are not pulmonary tuberculosis even when accompanied by a positive tuberculin test. A differential leukocyte count may give information that is not suspected and a second chest roentgenogram obtained two weeks after the first may establish the diagnosis. Many of the patients give a history of having had asthma. There is no reason thus far discovered why the two diseases may not be present at the same time. In asthma, the mucosa of the bronchial tree is the shock organ of the allergic reaction; in Löffler's syndrome, the parenchyma of the lung itself is considered, by most, to be the shock

organ. The possible infection of the intestines by intestinal parasites should always be considered. Of these, *ascaris lumbricoides, strongyloides, stircoralis, trichinella spiratis,* and *ancylostoma americanum* have been reported in Löffler's syndrome. Most of the cases so infected usually, but by no means invariably, give a characteristic history and clinical picture and these, together with the laboratory findings, are generally those of a condition much less benign than Löffler's syndrome. There is no specific treatment for Löffler's syndrome.

THERAPY

The allergen, when known, should be removed and cases of intestinal infection should be cleared of the infection by approved methods and treatment. Engel (4) recommended the use of calcium lactate, probably more for its psychotherapeutic effect than for any medicinal value. When one considers the probable allergic basis of this disease, it is surprising that so little has been written regarding the use of adrenalin in Löffler's syndrome. Broch (7), however, has reported a fatality where adrenalin was used. He attributed death to auricular fibrillation, brought about by a reflex action upon the heart.

CASE REPORTS

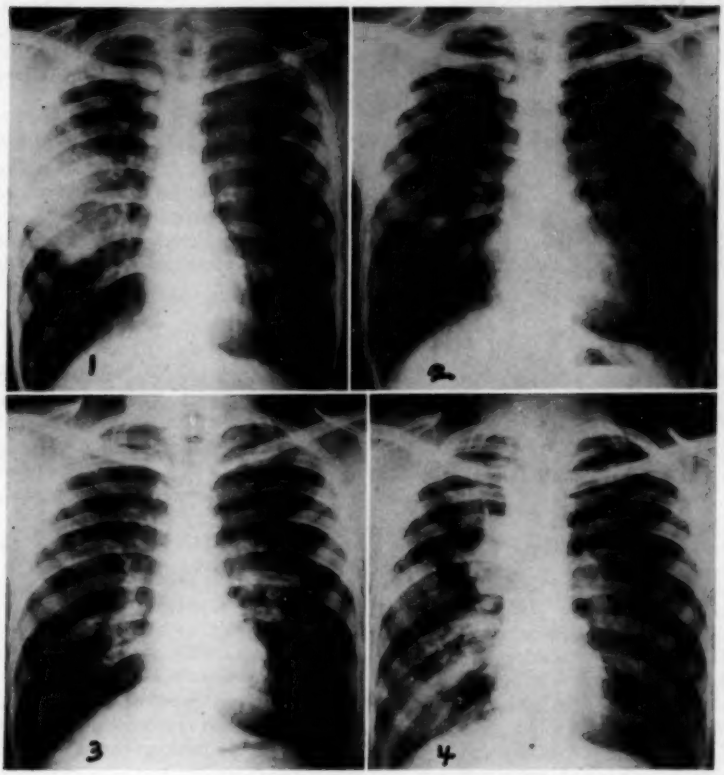
Case 1. R. F., a 23-year-old white male, a clerk by occupation, was referred to one of the writers (C. A. H.) February 28, 1947, because of a slight cough and wheezing in the chest. The patient was allergic to cheese, mushrooms, yeast, dust, and spring grasses. His temperature, pulse, and respirations were within normal limits. A chest roentgenogram taken at that time (figure 1) showed density in the right middle and lower lobes. The blood count revealed an eosinophilic percentage of 36. Repeated sputum examinations (random smears and concentrates) were negative for acid-fast bacilli, as were also laboratory examinations for intestinal parasites. The patient's cough disappeared on symptomatic treatment which did not include the use of antihistaminic agents, and a roentgenogram of the chest taken May 2, 1947 (figure 2), showed clearing of the right lung. A roentgenogram of the chest obtained January 13, 1948 (figure 3) revealed virtually normal lung fields. At no time did the patient appear at all ill.

He remained in good health until March 21, 1949, when he complained only of weight loss from 145 pounds to 118 pounds. A chest roentgenogram on that date (figure 4) showed involvement of the apex, the middle lobe, and the lower lobe of the right lung. He had a leukocytosis of 19,000 cells per cu. mm. of which 30 per cent were eosinophils. Numerous sputum studies (smears and concentrates) failed to reveal the presence of acid-fast bacilli. At the present time, May 26, 1949, the patient is under rest treatment and antihistaminics; the pulmonary densities have virtually disappeared. His weight taken April 26, 1949 was 130 pounds.

Comment: On the basis of the abnormalities in the first film alone (figure 1), one might well consider the possibility of the presence of a neoplasm since temperature, pulse, or respirations were not elevated and repeated sputum studies were negative for acid-fast bacilli. The eosinophilia of 36 per cent, however, was significant, the more so since laboratory studies were negative for intestinal parasites. The next two films (figures 2 and 3) should dispel any doubts as to the presence of any new growth. Examination of the fourth film (figure 4) suggests, in the light of the past history and laboratory findings, that the patient had again been exposed to some antigen to which he is hypersensitive. The seasonal incidence of the attacks (February 1947 and March 1949) may be of greater significance than purely coincidental occurrence.

Case 2. M. M., a white female, 31 years of age, was a nurse in a tuberculosis hospital. She had been under treatment at various times for allergic rhinitis. She developed marked

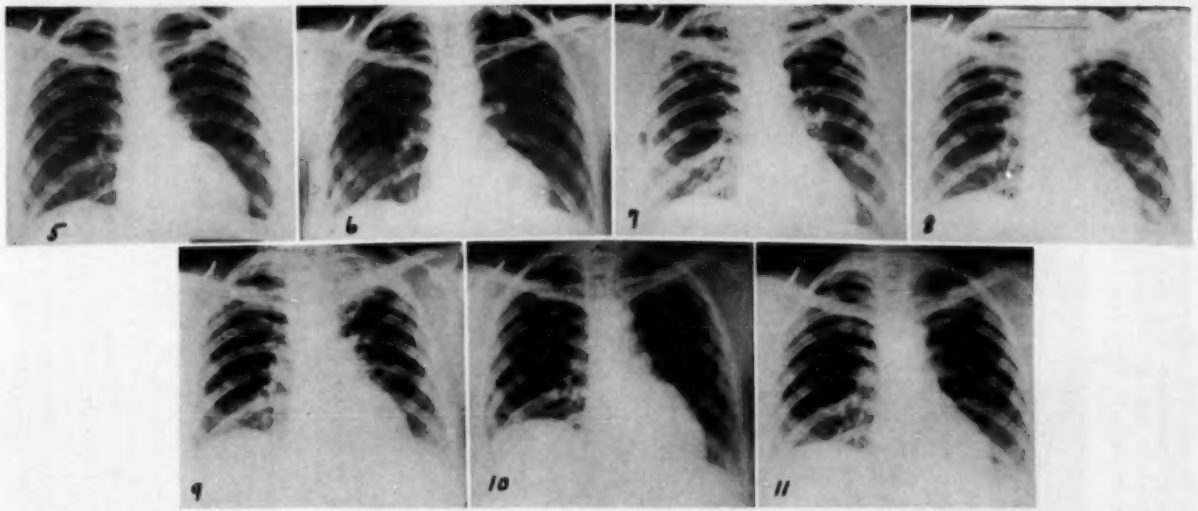
wheezing in the chest early in October 1944, while cleaning and storing the hospital blankets. Her temperature, pulse, and respirations were within normal limits. The blood count showed 4,000,000 erythrocytes per cu. mm., with a hemoglobin percentage of 75 and a total leukocyte count of 12,000 per cu. mm., of which 42 per cent were eosinophils. A routine



Case 1

FIG. 1. Roentgenogram taken February 28, 1947.
FIG. 2. Roentgenogram taken May 2, 1947.
FIG. 3. Roentgenogram taken January 13, 1948.
FIG. 4. Roentgenogram taken March 21, 1949.

roentgenogram taken at the time she was employed showed a virtually normal chest (figure 5). A roentgenogram taken at the time of her first symptom (figure 6) showed a pneumonitis at the base of the right lung. Repeated sputum studies (smears and concentrates) were negative for acid-fast bacilli; laboratory studies for intestinal parasites were not made. A film taken nine days after the onset of illness (figure 7) showed clearing of the lesion at the right base, but a roentgenogram taken three weeks later (figure 8) revealed a large area of density in the upper left lobe. At this point the patient was examined bronchoscopically



Case 2

[FIG. 5. Roentgenogram taken May 18, 1943.
FIG. 6. Roentgenogram taken October 9, 1944.
FIG. 7. Roentgenogram taken October 18, 1944.
FIG. 8. Roentgenogram taken November 9, 1944.
FIG. 9. Roentgenogram taken November 17, 1944.
FIG. 10. Roentgenogram taken December 19, 1944.
FIG. 11. Roentgenogram taken February 11, 1945.

and it was found that "the right lobe bronchus exhibited moderate inflammatory changes involving the mucosa" and "both main bronchi contained a quantity of thick mucoid secretions, which were negative for acid-fast bacilli on direct smear and by culture." Allergy tests were made and the patient was found to be sensitive to wool and coffee. Antihistaminics were given and rest was enforced. A film taken eight days after finding the density in the upper left lung (figure 9) showed clearing of the involvement. Subsequent roentgenograms of the chest (figures 10 and 11) showed clear lung fields. The patient has had routine roentgenograms of the chest every six months and there has been no recurrence of the disease to this date, May 26, 1949.

Comment: The fact that the patient was employed as a nurse in a tuberculosis hospital and had a normal chest roentgenogram at the time of her employment (figure 5) might well have justified at least a tentative diagnosis of pulmonary tuberculosis were it not for the 42 per cent eosinophilia when she was first seen. The presence of a neoplasm might also have been considered at that time but for the same reason. The changes in the subsequent three roentgenograms (figures 7, 8, and 9), however, proved the diagnosis of either pulmonary tuberculosis or new growth to have been untenable.

SUMMARY

Two cases of Löffler's syndrome believed to be of allergic origin have been presented. The value of a complete history and of repeated roentgenograms, as well as numerous examinations, has been shown. Löffler, in his two papers, described what constitutes the syndrome, and it is to be regretted that so many conditions bearing only superficial resemblance to the syndrome described by him have been subsequently reported. Löffler's syndrome is not a condition with many clinical manifestations and a single etiologic factor, but is more probably a syndrome of varied etiology.

SUMARIO

Síndrome de Löffler: Transitoria Infiltración Eosinofílica del Pulmón

Los 2 casos de síndrome de Löffler presentados parecen ser de naturaleza alérgica. Queda demostrado el valor de una anamnesia completa y radiografías repetidas, así como de muchos exámenes. Löffler, en sus dos trabajos, describió lo que constituye el síndrome, y es de lamentar que se hayan comunicado con ese nombre muchos estados que no guardan más que semejanza superficial con el síndrome en cuestión. No se trata de un estado con muchas manifestaciones clínicas y un solo factor etiológico, sino más probablemente de un síndrome que reconoce a veces etiología desconocida y varia.

RESUME

Syndrome de Löffler: Infiltrat pulmonaire labile temporaire avec éosinophilie

Deux cas de syndrome de Löffler qui, à notre avis, étaient d'origine allergique ont été présentés. La valeur d'une observation complète et de radiogrammes répétés, comme celle de nombreux examens, a été exposée. Dans ses deux communications, Löffler a décrit ce qui constitue ce syndrome et il y a lieu de regretter que tant de manifestations, n'ayant avec le syndrome décrit par lui que des traits de ressemblance superficiels, soient décrits sous le nom de syndrome de Löffler. Il ne s'agit pas d'une affection à manifestations cliniques variées avec facteur étiologique unique, mais plus vraisemblablement d'un syndrome dont l'étiologie est parfois inconnue et variée.

REFERENCES

(1) Löffler, M.: Zur Differential Diagnose der Lungeninfiltrierung, Beitr. z. Klin. d. Tuberk, 1932, *79*, 338.

(2) Löffler, M.: Die flüchtigen Lungininfiltrate mit Eosinophile, Schweiz. med. Wchnschr., 1936, *66*, 1069.

(3) Pierce, C. B., Crutchlow, E. F., Henderson, A. F., and McKay, J. W.: Transient focal pulmonary edema, 1945, *82*, 1.

(4) Engel D.: Oedema pulmonis allergium vernale: New disease of lungs, Chinese M. J., 1935, *49*, 1162.

(5) Alfers, I.: Loeffler's syndrome, J. Allergy, 1947, *18*, 39.

(6) v. Meyenburg, H.: Eosinophilic pulmonary infiltration: Pathology, anatomy, and pathogenesis, Schweiz. med. Wchnschr., 1942, *72*, 809.

(7) Brock, O. J.: Case of transient pulmonary infiltration with eosinophilia with fatal issue after treatment by adrenalin spray for asthma, Acta med. Scandinav., 1943, *113*, 310.

SENSITIVITY OF TUBERCLE BACILLI TO AMITHIOZONE (MYVIZONE)[1]

MOLLIE MOLLOV, IDA HILL, AND THADDEUS J. KOTT

(Received for publication December 7, 1950)

INTRODUCTION

Domagk has published evidence that the thiosemicarbazones are effective *in vitro* and *in vivo* against the tubercle bacilli and are also effective in tuberculosis produced experimentally in guinea pigs and rabbits (2). Much work with this agent has been done in Germany. Brecke and Boehm, in 5 cases, noted suspicious indications that thiosemicarbazone-resistant tubercle bacilli might have appeared, but no bacteriologic studies of sensitivity were made (4).

The present study was undertaken to determine whether tubercle bacilli will become resistant to amithiozone (Myvizone)[2] after patients had been treated daily with this compound over periods of two to four months with 200 to 400 mg. per day. The sensitivity of tubercle bacilli to Myvizone was determined on organisms obtained from a small series of patients who were studied for clinical and pharmacologic results of this drug, and have been reported by Simmons and his associates (8).

MATERIALS AND METHODS

Sputum was collected from 15 patients prior to institution of treatment and every two weeks during treatment. These specimens were digested with 4 per cent sodium hydroxide and neutralized with dilute hydrochloric acid. The sediments were cultured into Dubos liquid medium and on the classical egg-yolk-potato medium (9). The tubercle bacilli isolated were then grown in modified Kirchner's medium in which sorbitan mono-oleate has been replaced by Triton A-20 and from which the serum albumin and iron ammonium citrate have been omitted (7). The modified Kirchner medium was used also for the *in vitro* sensitivity tests of the tubercle bacilli to Myvizone.

The Myvizone standard contained 0.5 mg. of drug per ml. in triethylene glycol (30 per cent), was heated, then passed through a Seitz filter for sterilization. Ten Wassermann tubes were set up for the test. Varying amounts of Myvizone were added to the Kirchner broth so that the ten tubes contained the following number of γ per ml.: 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39, 0.19, 0.09. The tenth tube contained no drug. To each tube was added 0.2 ml. of a seven-to ten-day culture of the tubercle bacilli to be tested. The total volume in each tube was 2 ml. The tubes were then shaken and incubated for fourteen days, and were read on the seventh and fourteenth days.

The end point was regarded as the quantity of Myvizone added to the last clear tube before ± growth at the end of fourteen days of incubation.

RESULTS

The Myvizone sensitivities of the tubercle bacilli isolated prior to treatment and during two-week intervals of therapy are reported in table 1. In the 15 patients studied, the sensitivities of the bacilli discharged prior to treatment were about the same in all cases except in Case 13. With this exception, the tubercle

[1] From the Triboro and Queens General Hospitals, Jamaica, New York.

[2] Trade name of E. R. Squibb & Sons.

bacilli obtained were sensitive *in vitro* to between 0.09 γ per ml. to 0.39 γ of Myvisone per ml. The organisms from Case 13 were sensitive to 1.56 γ of drug per ml. of medium. During the fourteen- to sixteen-week treatment period there was no significant change in the *in vitro* drug sensitivities of the tubercle bacilli obtained from the patients save in one case. The tubercle bacilli discharged by this patient (Case 6) became more resistant to Myvisone, with a rise in inhibitory concentration from 0.09 to 3.12 γ per ml. of medium.

TABLE 1

Myvisone Sensitivity of Tubercle Bacilli Isolated Prior to Treatment, During Two-Week Intervals, and After Therapy

CASE	TOTAL MYVISONE ADMINISTERED	LENGTH OF TREATMENT	SENSITIVITY OF TUBERCLE BACILLI, γ/CC.						
			Before treatment	Number of weeks after first injection					After treatment
				2	4	6	8	10	12
	mg.	weeks							
1	49.4	16	.09	.78	1.56	—	—	—	<.09	<.09
2	49.4	16	<.09	<.09	<.09	.19	.19	—	—	<.09
3	49.4	16	<.09	—	—	<.09	—	—	.19	—
4	48.6	16	.39	.19	<.09	<.09	—	—	.19	.19
5	45.1	16	<.09	<.09	<.09	.19	—	—	<.09	<.09
6	34.3	16	<.09	<.09	—	<.09	—	—	<.09	3.12
7	25.8	16	<.09	—	.19	<.09	<.09	—	—	.19
8	40.8	12	<.09	—	<.09	<.09	—	<.09	—	.19
9	40.4	12	<.09	<.09	—	.39	—	—	—	<.09
10	27.9	12	.19	—	.19	<.09	—	—	—	<.09
11	17.5	12	—	.09	.78	<.09	—	—	—	<.09
12	7.67	10	.19	<.09	<.09	—	<.09	—	—	.39
13	32.2	9	1.56	3.12	.19	—	—	—	<.09	<.09
14	3.05	9	.39	<.09	<.09	.19	—	—	—	—
15	9.8	4	<.09	<.09	<.09	—	—	—	—	<.09

— = sensitivity not done.
< = less than.

COMMENT

According to Donovick and his associates (5), Myvisone is considered inactive if it does not inhibit tubercle bacilli at a concentration of 10 γ per ml.; active if it inhibits at a concentration of 1 to 10 γ per ml.; and highly active if it inhibits at a concentration of less than 1 γ.

SUMMARY

Strains of *M. tuberculosis* which were periodically isolated from 15 patients who were receiving amithiosone (Myvisone) were tested *in vitro* for susceptibility to the drug. The total period of therapy was: sixteen weeks for 7 patients; twelve weeks for 4 patients; ten weeks for one patient; nine weeks for 2 patients; and four weeks for one patient. There was only one instance of a change in drug susceptibility during treatment, and the degree of change in

this case was not great. It is possible that the emergence of drug-resistant tubercle bacilli might become a problem on longer periods of thiosemicarbazone therapy.

Acknowledgment

The writers wish to thank Dr. Alfred Angrist, Director of Laboratories of Triboro and Queens General Hospitals, for his suggestions in this study and for reviewing the manuscript.

REFERENCES

(1) Behnisch, R., Mietzsch, F., and Schmidt, H.: Chemical studies on thiosemicarbazones with particular reference to antituberculous activity, Am. Rev. Tuberc., 1950, *61*, 1.

(2) Domagk, G.: Investigations on the antituberculous activity of the thiosemicarbazones *in vitro* and *in vivo*, Am. Rev. Tuberc., 1950, *61*, 8.

(3) Mertens, A., and Bunge, R.: The present status of the chemotherapy of tuberculosis with Conteben, a substance of the thiosemicarbazone series: A review, Am. Rev. Tuberc., 1950, *61*, 20.

(4) Hinshaw, H. C., and McDermott, W.: Thiosemicarbazone therapy of tuberculosis in humans, Am. Rev. Tuberc., 1950, *61*, 145.

(5) Donovick, R., Pansy, F., Stryker, G., and Bernstein J.: The chemotherapy of experimental tuberculosis: I. The *in vitro* activity of thiosemicarbazides, thiosemicarbazones and related compounds, J. Bact., 1950, *59*, 667.

(6) Hamre, D., Bernstein J., and Donovick, R.: The chemotherapy of experimental tuberculosis. II. Thiosemicarbazones and analogues in experimental tuberculosis in the mouse, J. Bact., 1950, *59*, 675.

(7) Rake, G., Jambor, W. P., McKee, C. M., Pansy, F., Wiselogle, F. Y., and Donovick, R.: The use of the mouse in a standardized test for antituberculous activity of compounds of natural or synthetic origin: III. The standardized test, Am. Rev. Tuberc., 1949, *60*, 121.

(8) Simmons, G., Hobson, L. B., Resnick, A., DeNicola, R., and Bennett, R. H.: Human pharmacology of *p*-formylacetanilide thiosemicarbazone (Myvizone), Am. Rev. Tuberc., 1950, *62*, 128.

(9) Mollov, M., and Oshinsky, A.: Value of Dubos' medium in tests for streptomycin sensitivity of *Mycobacterium tuberculosis*, Am. J. Clin. Path., 1949, *19*, 67.

Correspondence

CHEMOTHERAPY FOR ALL ACTIVE TUBERCULOSIS

To the Editors of the American Review of Tuberculosis:

The use of tuberculostatic agents need no longer be restricted because of scarcity, cost, or the toxicity resulting from impure preparations or excessive dosage (Dis. of Chest, 1949, *16*, 761). Nevertheless, many writers still urge withholding chemotherapy in the absence of obvious and urgent indications in order to avoid the development of bacillary resistance against streptomycin, which would preclude its utilization in the treatment of later acute tuberculous complications and in prophylaxis with resectional surgery (Am. Rev. Tuberc., 1950, *61*, 436). Additional chemotherapeutic resources, however, are available for patients in whom resistance to one agent has developed (Am. Rev. Tuberc., 1950, *61*, 226) and new methods of administration have greatly reduced the incidence of resistant forms (Minutes of Eighth Streptomycin Conference, Veterans Administration, Atlanta, Ga., November 10, 1949, p. 87). Only a small minority of patients show predominantly resistant tubercle bacilli after three months of intermittent streptomycin treatment combined with para-aminosalicylic acid (Minutes of Ninth Streptomycin Conference, St. Louis, Mo., April 20, 1950, p. 205). It seems proper, therefore, to consider extending the utilization of specific treatment for tuberculosis.

All chemotherapeutic agents against tuberculosis so far available are bacteriostatic, not bactericidal. They are useless, therefore, in instances where tubercle bacilli are not multiplying in the body. When tuberculous lesions, either of primary or reinfection type, have become arrested or inactive, whether with resorption, encapsulation, or fibrous replacement, tuberculostatic agents are superfluous, as nature has already stopped the multiplication of the bacilli.

Prophylactic injection of streptomycin before infection has no effect on the later development of the disease in guinea pigs. Continuous administration of adequate dosage of antibiotics may avert or ameliorate exacerbations or reinfections, but its expense and inconvenience and occasional toxicity and allergic sensitization, rather than the possible production of resistant strains, militate against its general use for this purpose.

In old, stable "good chronic" cases with cavitation but no active inflammatory component, bacilli growing in cavities may sometimes be expectorated without development of metastatic lesions within the body. Slow progression or acute exacerbations, however, frequently occur in apparently stationary chronic cases, and the possibilities of active treatment should not be neglected. Unless mechanical measures are taken to close such cavities, chemotherapy is futile and only leads to the development of resistant bacilli.

Patients with primary or reinfection tuberculosis of minimal extent, or even with moderately or far advanced tuberculosis in which no open cavities are present, but in whom some exudative or inflammatory processes still remain active, might well be given courses of chemotherapy. Even though the prognosis is excellent and chemotherapy may be of relatively little importance in such patients, it may be well to take advantage of additional support which might be given to the natural healing tendencies of the body. Resistant forms appear much less frequently in such cases than in open cavity cases (Am. Rev. Tuberc., 1949, *59*, 402) while, on the other hand, the chances of complications developing which will require later administration of the treatment are relatively slight.

Most patients with active advanced tuberculosis could receive chemotherapy as well as some form of collapse therapy. Undue parsimony may actually prove wasteful in the long run. Timing is important. The treatment should not be deferred too long, lest the optimum time for its effect may be passed. It is particularly important that treatment be given early in cases of aspiration and bronchogenic spreads, such as those following hemorrhage or operative procedures, before extensive caseation and cavitation may occur.

Most patients with cavities require some form of collapse therapy, but this should generally be supplemented by simultaneous chemotherapy. Too great an interval should not be allowed to intervene between starting the two forms of treatment. Not only are complications diminished, but the healing may be accelerated and the eventual therapeutic effect enhanced by the combination.

Reserving chemotherapy for its possible future use in connection with surgical procedures may forfeit its greatest value. Prophylactic streptomycin with surgery is given chiefly to the few patients who receive resections or other extensive operative procedures or to those with a particularly poor preoperative prognosis. Even if resectional surgery is given without chemotherapy, only few patients suffer from spreads or other complications, and these often respond to other measures without the need for chemotherapy. The incidence of postoperative complications and deaths is greater in patients who had previously received courses of chemotherapy than in those who had not had such treatment. Some of this excess, however, results from the selection of unfavorable cases following unsuccessful treatment rather than from the development of resistant bacilli. Few patients develop miliary or meningeal spreads requiring chemotherapy and even with it only too many of the latter eventually succumb. Patients should not be deprived of needed chemotherapy merely in order to have it available for such possible but improbable future eventualities.

Patients with far advanced, extensive, and pre-terminal disease, with numerous cavities and caseation as well as exudative lesions, cannot be cured by chemotherapy alone. However, they may often be given a more favorable outlook and brought within the purview of collapse therapy following improvement with chemotherapy and rest. Even if the ultimate prognosis remains bad, they may have their lives prolonged and suffering relieved by the use of these agents. Although the administration of chemotherapy here may make it unavailable later, patients who without it may never survive to avail themselves of its hypothetical future benefits, if they do respond, may never actually need it again.

In patients with old fibrotic disease, whose cavities may have been apparently closed by collapse measures, residual parenchymal or bronchial lesions may give rise to intermittent rare bacilli on sputum or gastric cultures. Complete and permanent healing with lasting sputum conversion and lessened fear of recurrence often follows courses of chemotherapy in such cases. The danger of development of resistant forms of tubercle bacilli still exists, but this should not preclude the use of streptomycin in cases where it may be of value. The best protection for the patient himself against resistant forms of tubercle bacilli is the most effective treatment of the tuberculous lesions in his body. The best protection of the public from the transmission of streptomycin-resistant bacilli lies in preventing the spread of all tubercle bacilli, whether sensitive or resistant (J. A. M. A., 1948, *136*, 490).

Chemotherapy should not be wasted by administration without needed concomitant measures. Ambulatory treatment of active tuberculosis, neglect of complications, failure to use pneumothorax or pneumoperitoneum, or surgical collapse, drainage, or resectional measures when indicated are unfortunately only too often observed. Improper dosage or use of a single chemotherapeutic agent at a time is to be deplored. But it is the delay in the use of collapse, not the premature use of chemotherapy, which is most often repre-

hensible. The therapeutic armamentarium of modern phthisiology may be properly realized only when it is vigorously applied, not held indefinitely in reserve. The parable of the talents (Matthew, Chapter 25, Verses 14–30) may well be applicable to modern phthisiology.

EMIL BOGEN AND
WILLIAM H. OATWAY, JR.

Olive View, California
December 6, 1950

To the Editors of the American Review of Tuberculosis:

The writer has taken over the job of finishing the book, *Autobiographical Sketches of Disease by Physicians*, which was started by the late Dr. Max Pinner. Because of his many years of illness from heart disease, Doctor Pinner became interested in how much he had learned about his malady which did not appear in the usual medical texts. He also became fascinated by how much one learns about adaptation to a chronic illness. Doctor Pinner believed that his "education" was not unique, and that many other physicians who had experienced illness would have as much to contribute. He accordingly began to collect autobiographical sketches from physicians with the idea of publishing a book containing approximately fifty contributions.

At the time of his death, Doctor Pinner had obtained about twenty excellent sketches. It seemed a pity that such a valuable manuscript should be discarded, and his widow appealed to me to finish the book. I have been happy to take over as associate editor, leaving Doctor Pinner's name as senior editor.

I hope the book will represent a genuine contribution to the understanding of disease for physicians and medical students (and also, I believe, for nurses, psychologists, social workers, et cetera.)

W. W. Norton and Company have agreed to publish the book.

I would welcome correspondence from physicians who would like to contribute essays to Doctor Pinner's book. The essays can be written anonymously if the author prefers that arrangement.

There is a particular need for essays in the following fields: malignant disease, emotional breakdown with recovery, drug addiction, partial or complete loss of vision or hearing. Most of the essays are averaging approximately 3,000 words. Essays on other disabilities can still be given consideration.

BENJAMIN F. MILLER

Massachusetts General Hospital
Boston 14, Massachusetts
January 15, 1951

BOOKS

JOHN B. MCDOUGALL: *Tuberculosis. A Global Study in Social Pathology. Pp. viii–455, Williams & Wilkins Company, Baltimore, 1949, $6.00.*

There has long been need for a book of this character devoted to the epidemiology of tuberculosis rather than to its pathogenesis and clinical aspects. The author, writing from a broad background of close contact with tuberculosis and more recently from experience in the international field, has correctly labelled his volume a *Global Study in Social Pathology*. He has foregone the usual and familiar consideration of the biology of the tubercle bacillus, the gross and microscopic pathologic manifestations, the details of symptoms and physical findings, or the mechanisms of treatment. All of these have been neglected in favor of a discussion of the occurrence of tuberculosis, the factors governing its prevalence, and the programs most likely to produce control.

The first third of the volume is devoted to a consideration of the occurrence of tuberculosis in various countries. Arranging the countries by continents, the author presents significant facts and comments regarding the known prevalence of tuberculosis in each country, some of the factors responsible for the various rates, and the control measures used. The reader who has a broader interest in tuberculosis than the narrow confines of his own country and who is interested in the influence of varied social and economic influences will find this section a veritable gold mine of information not previously brought together within a single volume. Doubtless many who are familiar with any particular country will find inadequacies and will wish that the author had used, or had had access to, many data locally available. This is inevitable, for no one can be expected to have complete familiarity with the vagaries of tuberculosis in several hundred widely scattered and differing localities. The reader who will note such inadequacies with respect to his own country must not, however, lose sight of the fact that the material here compiled represents an herculean task and makes readily available data heretofore widely scattered.

The second third of the volume deals with epidemiologic significance of certain factors that govern the morbidity and mortality rates for tuberculosis. Considered here are such factors as age, migration, resistance, infecting dose, and heredity. The author labels this as a summary of prevailing views. Those views are presented concisely and impartially, although the author properly is not hesitant to express his own evaluations of conflicting data.

The remaining third of the volume is devoted to the development of control programs. The author first considers methods used in evaluating the tuberculosis problem of a given area. A schedule for use in such evaluation is presented with extensive comments on each of the various items included. As a part of these comments there are valuable discussions of such factors as race, housing, nutrition, and economic factors as they condition the tuberculosis situation of any country. A most valuable section here is that devoted to results of mass radiography in various countries.

Criticism of any book is easy, especially in a field so controversial as tuberculosis. Many readers will differ with some of McDougall's views; especially is this true of those who are the ardent protagonists of any particular doctrine or control measure. Such ready criticism should not blind the reader to the fact that the author has produced here a volume of immense value to all who are interested in the broader aspects of tuberculosis as a world problem as well as to those who seek an impartial and concise epidemiologic appraisal.

GAYLORD W. ANDERSON

JACOB JESSE SINGER: *Differential Diagnosis of Chest Diseases. Pp. 334 with illustrations, Lea & Febiger, Philadelphia, 1949, $7.50.*

The author has written this book primarily to give the general practitioner an outline of the essentials of diagnosis of chest diseases. He stresses the importance of an adequate history and physical examination. He also describes the various laboratory and roentgenographic procedures that are useful in establishing a diagnosis. A concise review of the various abnormalities and diseases of the thoracic cage, pleura, mediastinum, diaphragm, tracheobronchial tree, and lungs is given. Whenever controversial issues regarding any one pathologic condition have been encountered, the author has indicated what his opinion is, with the idea of avoiding too much confusion on the part of the reader. He admits that such a procedure might possibly lead to error. He feels, however, that this approach is preferable to presenting controversial points.

The book is generously illustrated with roentgenographic studies revealing various pathologic processes. It also contains numerous drawings showing anatomic relationships in normal, as well as abnormal, states. It is a book written primarily to aid in diagnosis and consequently its one deficiency as a complete textbook on diseases of the chest is that it mentions practically nothing about therapy.

This book is well written and would make a valuable addition to any physician's library.

H. W. SCHMIDT

CARL-AXEL ADAMSON: *A Bacteriologic Study of Lymph Nodes (Analysis of Post-mortem Specimens with Particular Reference to Clinical, Serological, and Histopathological Findings), Acta medica Scandinavica, 1949, volume 133, supplement 227, pp. 172.*

This study consists of the results of bacteriologic and histopathologic examination of cervical, mediastinal, and abdominal lymph nodes. Tonsils and spleens were studied in similar fashion and, in addition, cultures were taken from the mucosa of the respiratory tract. The observations were made on a series of 106 autopsies. The material was divided into groups for study according to the clinical diagnosis of tuberculosis, nontuberculous infection, noninfectious illness, and a group of "normals" who died abruptly from traumatic or toxic causes. In a large number of cases, serologic tests were made pre- and post-mortem, primarily in relation to streptococcal and staphylococcal infections (antistreptolysin and anti-staphylolysin titrations).

Five or six different species were cultured from most necropsies, with the greatest variety obtained from the mucosal surfaces of the respiratory tract. The "normal" cases revealed a much lower frequency of infection of lymph nodes and spleen than did cases with known infections. The pathogenic or potentially pathogenic bacteria isolated in greatest numbers were *Staphylococci*, *Streptococci*, tubercule bacilli, and coliform organisms. A smaller number of pneumococci were isolated.

It was found that a definite relationship existed between the presence of *Staphylococci* at post-mortem and an increased anti-staphylolysin titer during the six months preceding death. It was evident that the elevation of titer was greatest in those cases where the *Staphylococci* were not only situated superficially on mucous membranes but were also found deep in the body in lymph nodes and spleen. A similar situation existed with regard to anti-streptolysin titers with the exception that the presence of streptolysin-producing *Streptococci* only on tonsils or mucous membranes was associated with high titers of antibody without the requirement of penetration into deeper structures such as was the case with *Staphylococcus* infections. Thus, the finding of elevated antibody titers several months

before death to *Staphylococcus* and *Streptococcus* infections present at post mortem indicated that these infections had existed for a considerable time before death.

Tubercle bacilli were isolated only from cases in which that diagnosis had been made clinically. A concomitant observation in the group with tuberculosis was a high incidence of multiple infections in lymph nodes and respiratory tract. *Staphylococcus aureus*, *Streptococci*, coliform organisms, and pneumococci were the principal associated offending strains. These organisms were found in greater frequency in the group with tuberculosis than in the cases without clinical infection. Furthermore, the frequency of these bacteria in the tuberculosis cases was on the whole greater than, or equal to, that noted in the groups containing cases of clinical infections without tuberculosis. Serologic evidence of the presence of these organisms before death was obtained in some cases infected with *Staphylococcus aureus*, *Streptococci*, and pneumococci.

Histopathologic examination revealed good correlation between the presence of infection by cultural examination and the occurrence of lymphadenitis. A plasma cell reaction in the lymph nodes was found to be significantly correlated with increased anti-streptolysin titers (streptococcal infection), while sinus catarrh (sinus congestion with phagocytic mononuclear cells) was found to be clearly correlated with increased anti-staphylolysin titers (staphylococcal infection). There was, in general, close correlation between cultural and histopathologic evidence of tuberculosis. No conclusions were drawn regarding the observations in a moderate number of cases which had been treated with sulfonamides and penicillin.

VERNON KNIGHT

AMERICAN TRUDEAU SOCIETY

Medical Section of the National Tuberculosis Association

Reports of the Clinical and Laboratory Subcommittees

CLINICAL SUBCOMMITTEE

The Clinical Subcommittee met at the Hotel Statler, New York, N. Y., on November 14 and 15, 1950, and held a joint session with the Laboratory Subcommittee on the morning of November 15. Members of the Clinical Subcommittee present were: Drs. David T. Carr, H. H. Fellows, H. Corwin Hinshaw, Daniel E. Jenkins, William M. M. Kirby, Carl W. Tempel, John W. Trenis, Norman J. Wilson, and William B. Tucker, Chairman. Also present as guests were Dr. Grover C. Bellinger, President, American Trudeau Society, Dr. H. McLeod Riggins, Chairman, Committee on Medical Research and Therapy, Dr. William S. Tillett, Dr. Gardner Middlebrook, Dr. David T. Smith, President, National Tuberculosis Association, Dr. Floyd M. Feldmann, Mr. William Steenken, Jr., and Miss Bernadette Rogers.

The Clinical Subcommittee considered the following subjects, and took the following actions:

1. *A proposal that the American Trudeau Society sponsor regional interstate conferences similar to those which have been held at Pembine, Wisconsin.*

The success in recent years of the regional interstate tuberculosis conferences held annually at Pembine, Wisconsin, has prompted the Clinical Subcommittee to recommend to the Committee on Medical Research and Therapy that the American Trudeau Society sponsor a program which will further the purpose and engender the spread of similar conferences throughout the country. It is the feeling of the Subcommittee that such conferences would help to promote freer interchange of ideas among physicians about the treatment of tuberculosis, minimize regional eccentricities of therapy, and enhance broader acquaintance and good fellowship among physicians living in the same area. In addition, with the more intimate intellectual contact which these limited and informal conferences enjoy, considerable knowledge of current practices at the patient level could be acquired by the physician.

It is anticipated that the motivating interest for such conferences will be local and regional, but the New York office could be of assistance to the local organizations in matters of administration as well as in a limited financial capacity. Joint sponsorship with local and state agencies, or with the Veterans Administration, would be helpful in some areas, while in others financing an invited speaker or the participation in the program of an outstanding hospital from an adjacent locality would successfully augment local efforts.

The Clinical Subcommittee therefore recommends to the Committee on Medical Research and Therapy that it take such steps as may be indicated to implement such a program, and suggests that the parent Committee confer with the Committee on Medical Education as to possible mutual interests in this venture.

2. *The undertaking of a project for the gathering of data on the results of different forms of therapy of pulmonary tuberculosis.*

The Subcommittee felt that there exists a need for gathering data on this subject on as objective a basis as possible from as wide a variety of sources as possible, not so much

with the intention of undertaking a definitive analysis of the effects of different variables of therapy in the outcome of such treatment as in lessening the differences in reporting of results from different sections of the country. It was called to the attention of the Subcommittee that results of therapy, as of artificial pneumothorax, vary widely in the literature making it impossible accurately to compare the factors responsible for the differences in results reported. The Subcommittee felt that, even short of the ultimate definitive study which could be undertaken only by the most careful planning and projected many years into the future, there is sufficient merit in a cooperative collecting of data along these lines to warrant the Society's undertaking such a project.

The Subcommittee therefore recommends to the Committee on Medical Research and Therapy that there be appointed for the year 1951–1952 a special subcommittee concerned solely with this problem, for the further study of the details involved and its practicability. It is believed to be desirable that included in the membership of such a special subcommittee there be (a) individuals experienced in the gathering of such clinical data on a wide scale, (b) at least one thoracic surgeon interested in the problem, (c) an individual trained in statistical procedures of this nature, and (d) representatives of at least one or two institutions which might indicate their willingness to cooperate in such a study.

There were called to the attention of the Clinical Subcommittee two considerable groups of clinical material which would be available: (*1*) approximately 1,100 cases treated by the Metropolitan Life Insurance Company at Mount McGregor, with approximately 98 per cent follow-up, and (*2*) approximately 7,000 cases at Battey State Hospital, Rome, Georgia, with approximately 80 per cent follow-up. The Subcommittee believes that undoubtedly a sufficient number of other groups exist where there is the willingness to cooperate to make such a project practicable.

In the discussion of this undertaking the Subcommittee was convinced that it was feasible only if there was the most careful compromise between, on the one hand, a minimum of data requested of cooperating institutions, and, on the other, data adequate for answering the more important questions as to the results of the variables of therapy. The Subcommittee believes that the special subcommittee, if its establishment is approved, will be interested in considering inclusion of:

Identifying data: name, institution, number, et cetera
Data classifying patient: age, sex, race
Data classifying the disease: stage, duration, character
Variables of therapy: collapse/surgery, bed rest, drugs, patient cooperation
Results of therapy: X-ray change, sputum status, survival, relapse (and readmission to hospital), an "over-all" rating of the effect of therapy, and working capacity.

3. *The preparation of a revised statement on the current status of drug therapy in tuberculosis.*

The Subcommittee believed that a number of new developments in this field, since the statement prepared a year ago by the Clinical Subcommittee was published in the March 1950 issue of *The American Review of Tuberculosis*, justified this Subcommittee's undertaking a revision for the guidance of the membership of the Society and others interested in this aspect of the treatment of tuberculosis. The Subcommittee decided, however, that it was not prepared at this time to complete the preparation of such a statement, and is deferring the undertaking until later in the year.[1] In preliminary discussion of the matter, however, the Subcommittee did indicate that it proposes recommending for the standard therapy of a case of tuberculosis, in which indications for drug treatment exist, a combination of daily para-aminosalicylic acid and so-called "intermittent" streptomycin or

[1] To be published in the May 1951 issue of THE AMERICAN REVIEW OF TUBERCULOSIS.

dihydrostreptomycin, i.e., SM or DHSM given every two or three days; that the dosage of PAS be 12–15 grams a day, including parenteral administration if not well tolerated orally, and SM/DHSM, 1 gram per treatment day—except in emergent tuberculous conditions where higher doses of SM or DHSM would be indicated. It is proposed that when the statement is prepared it include reference to the following:

Various forms of PAS administration
The relative merits of streptomycin and dihydrostreptomycin
Recommendations for different tuberculous conditions
Possible indications for drug therapy of minimal pulmonary tuberculosis and pleural effusion
Coverage for different thoracic surgical procedures
Indications for administration of PAS alone, both in patients with streptomycin-sensitive and streptomycin-resistant organisms
Brief reference to the present place in drug therapy of tuberculosis of such newer antituberculous agents as the thiosemicarbasones, terramycin, neomycin, viomycin, and mycomycin.

4. *A recommendation for transmission to the Annual Meeting Program Committee of the American Trudeau Society.*

The Clinical Subcommittee felt that it would further the aims of the Society to provide at the time of its annual meetings for greater discussion of important topics of timely interest by the planning of carefully constructed symposiums, centering around several presentations by leading investigators in the field and permitting a considerable degree of discussion from the floor. The Subcommittee felt that this need is not met by the practice, on the one hand, of formal planned discussion of formal papers, or that, on the other, of brief morning symposiums of one hour's length.

The Clinical Subcommittee requests of the Committee on Medical Research and Therapy that it pass on through suitable channels to the Annual Meeting Program Committee and the officers of the Society the feelings of the Clinical Subcommittee in this matter.

5. *The question of the problem of the disposition of the so-called "good chronic" patient with tuberculosis, with a "positive" sputum.*

The Subcommittee did not believe that in the time available it could do justice to this subject, but *did recommend to the Committee on Medical Research and Therapy that it suggest to next year's Clinical Subcommittee that this subject appears to be one worthy of discussion, perhaps leading to specific recommendations.*

LABORATORY SUBCOMMITTEE

The Laboratory Subcommittee met at the Hotel Statler, New York, N. Y. on November 15, 1950, and held a joint session with the Clinical Subcommittee in the morning. Members of the Laboratory Subcommittee present were: Dr. Martin M. Cummings, Dr. E. P. K. Fenger, Dr. Stuart Mudd, Dr. Gwyn Roberts, Dr. W. C. Workman, Dr. Guy P. Youmans, and Mr. William Steenken, Jr., Chairman. Guests present were: Dr. David T. Smith, President of the National Tuberculosis Association, and Dr. Gardner Middlebrook.

In the morning the Laboratory Subcommittee met jointly with the Clinical Subcommittee for the purpose of discussing problems that have clinical and laboratory significance in the diagnosis and treatment of tuberculosis. The discussion and action of the two Subcommittees in joint session will be found in the following pages.

In the afternoon the Laboratory Subcommittee met alone and continued the discussion

of bacterial resistance to streptomycin in the hope that it might agree on some standard method of reporting *in vitro* tests of resistance as a guide to the clinician. In this connection, the Subcommittee recommended that the report of a previous Laboratory Subcommittee meeting in 1948 on streptomycin-sensitivity tests be revised and published. The Clinical Subcommittee will be asked to suggest any changes or modifications in this report which may clarify the issue.

The status of the newer antibiotics was discussed and it was agreed that, since tuberculostatic activity varies with different species of animals, it would not be wise to state definitely that a given drug had antituberculous activity in general without specifying the animal in which the agent was being evaluated. It was the general opinion, however, that the tubercle bacillus does become resistant to streptomycin, neomycin, amithiozone (TB 1), viomycin, and para-aminosalicylic acid. To date, resistance to terramycin has not been established. It was reported that both guinea pigs and mice could tolerate viomycin in exceedingly high dosage without undue toxicity.

The Subcommittee recommended that institutions equipped to perform streptomycin-sensitivity tests do them on all patients admitted to the hospital in order to gain useful epidemiological information in studying contacts, et cetera.

In view of the observation that patients receiving combined treatment may convert their sputum early and have a period of negative cultures while on treatment and for some time after therapy has been discontinued, the question arose as to what constitutes a negative sputum and a negative gastric lavage. The suggestion was made that a period of time should elapse after cessation of treatment before obtaining the three consecutive sputum or gastric specimens prior to discharge. The time interval was not settled and is to be decided upon by a future joint meeting of the Clinical and Laboratory Subcommittees.

Several members of the former Subcommittee on Immunology, who now serve on the Laboratory Subcommittee, suggested that it would be helpful to have the Laboratory Subcommittee consider the bacteriological and immunological aspects of immunizing agents to be used as preventive measures in tuberculosis, such as BCG, heat-killed tubercle bacilli, irradiated tubercle bacilli, and other attenuated forms of the organism. This subject will be considered in detail at the next Subcommittee meeting, after which a recommendation will be submitted to the parent Committee.

The Subcommittee recommended that more long-term research be encouraged in the field of biochemical characteristics of bacterial resistance to antibiotics. In this regard the work should be done in institutions where the bacteriology of the tubercle bacillus is well understood.

JOINT MEETING OF CLINICAL AND LABORATORY SUBCOMMITTEES

In joint session the two Subcommittees considered the following subjects, with the following resulting actions:

1. *The employment of ACTH and cortisone in the treatment of patients with tuberculosis.*

After careful consideration of the evidence available, and recognizing the preliminary state of investigations in this field, the two Subcommittees nevertheless felt that apparent trends are of sufficient importance to warrant the issuance of a statement for guidance of members of the American Trudeau Society. *The two Subcommittees voted unanimously to recommend the issuance of a news release to read as follows:*

Because the action of ACTH and cortisone upon the factors of resistance to tuberculosis has been shown to be deleterious in at least three species of experimental animals and there

is strongly suggestive evidence along the same lines in human beings, it is recommended that these substances *not* be used in patients with active tuberculosis, and that they be used with extreme caution in human beings with possibly latent tuberculous infection, until further investigative work has shown that such administration may be safe. The routine diagnostic examination for tuberculosis of patients under physicians' care is especially necessary for patients who are being considered for ACTH or cortisone therapy.

2. *The hemagglutination test.*

The two Subcommittees recommended unanimously to the Society the following statement:

The hemagglutination reactions in the hands of a number of investigators have been shown to possess considerable promise in the study of the immunologic processes of tuberculosis. At the present time it is not felt that these tests have been sufficiently standardized and simplified to have diagnostic applications, or to be ready for routine clinical use. It is believed, however, that these tests contribute information of interest in the interpretation of immunologic processes in tuberculosis, and the Subcommittees desire to encourage the further investigation of the possible application of these tests.

3. *The question of the correlation of in vitro and in vivo determinations of bacterial resistance to streptomycin*, particularly as to whether the degree of resistance to streptomycin is determined *in vitro* may be accepted as representing resistance to streptomycin in man, as a guide, for example, to the continued use of streptomycin therapy.

The Subcommittees did not believe that they had sufficient data on this subject on which to base a statement or recommendation.

4. *The desirability of planning joint sessions of the Clinical and Laboratory Subcommittees in the future.*

It was the unanimous feeling of the membership of both Subcommittees that the joint session had been very worth while, and that there are likely to be annually a number of problems called to the attention of these Subcommittees which make it desirable that there be joint consideration by the combined membership.

The two Subcommittees therefore recommend to the Committee on Medical Research and Therapy that it be a part of the plan for each year's Subcommittee meetings that there be provision for such joint sessions.

Respectfully submitted,

David T. Carr, M.D.
H. H. Fellows, M.D.
H. Corwin Hinshaw, M.D.
Daniel E. Jenkins, M.D.
William M. M. Kirby, M.D.
Carl W. Tempel, M.D.
John W. Trenis, M.D.
Norman J. Wilson, M.D.

William B. Tucker, M.D., *Chairman*
Clinical Subcommittee

Martin M. Cummings, M.D.
E. P. K. Fenger, M.D.
Stuart Mudd, M.D.
Gwyn Roberts, M.D.
W. C. Workman, M.D.
Guy P. Youmans, M.D.

William Steenken, Jr., *Chairman*
Laboratory Subcommittee

THE AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

Edited by LAWRENCE B. HOBSON

VOLUME 63 APRIL, 1951 ABST. No. 4

CLINICAL STUDIES, TUBERCULOSIS

Miliary Tuberculosis of the Liver.—In 3 cases of miliary tuberculosis of the liver the diagnosis had not been established clinically, bacteriologically, or radiographically prior to needle biopsy of the liver. Idiopathic hyperpyrexia was the presenting problem in 2 of the cases; in the third, fever and jaundice were the salient features. Needle biopsy of the liver is suggested as a relatively safe and simple procedure to aid in the diagnosis of miliary tuberculosis of the liver. The procedure affords precise information concerning structural changes in the liver but as in any pathologic process of localized or patchy distribution only a positive microscopic finding is significant. It is suggested that miliary tuberculosis of the liver may be a more common disease entity than is clinically recognized. The response to streptomycin was gratifying in only one of these 3 cases.—*Miliary tuberculosis of the liver: Liver biopsy as an adjunct to diagnosis, M. M. Mansuy & W. J. Seiferth, Am. J. M. Sc., September, 1950, 220: 293.* (*W. J. Steininger*)

Sternal Marrow in Children.—Bone marrow was obtained by sternal puncture from 32 infants and children with medical and surgical tuberculosis. Six had miliary tuberculosis shown by roentgenograms. In no case was it possible to demonstrate the tubercles described in adults. Sternal marrow puncture by the method used is of no value in the diagnosis of tuberculosis in children.—*Sternal marrow puncture in the diagnosis of miliary tuberculosis in children, J. Wilson, Canad. M. A. J., November, 1950, 63: 504.*—(*T. H. Noehren*)

Spleen and Liver Tuberculosis.—The close vascular and lymphatic connections between the spleen and the liver account for the pathological correlations between the two organs. Tuberculosis in these organs may be of hematogenous origin, but there is evidence that active abdominal lymph node tuberculosis may also be the source of infection. Two cases of tuberculous splenomegaly were studied at autopsy; the liver showed secondary degenerative, sclerotic, and specific granulomatous changes. The secondary nature of these changes was confirmed by the presence of tuberculosis in the splenic veins and by the location of the liver lesions in the portal spaces and along the interlobular veins. A less common occurrence is described in a third case, where the liver was the site of the first tuberculous involvement and the splenic changes followed later. Similar cases are on record in the literature. Experimental studies also showed the possibility of splenic lesions following a liver involvement.—*Sulla tubercolosi associata del fegato e della milza: Contributo anatomoclinico alla conoscenza delle forme splenopatiche ad epatolienali, E. Miceli, Arch. E. Maragliano, May-June, 1950, 5: 421.*—(*L. Molnar*)

Disseminated Bone Tuberculosis.—The term osteitis tuberculosa multiplex cystoides has led to much confusion. It is suggested that the term disseminated bone tuberculosis be substituted for cases of widespread tuberculous bone involvement with or without a cystic appearance. In an adult patient with disseminated bone tuberculosis with more extensive lesions than have been reported previously, there were areas of bone destruction in the skull, the cervical spine, the dorsal spine, the lumbar spine, the left ilium, the left scapula, and multiple ribs. Biopsy of a spinous process afforded histologic and bacteriologic proof of

the tuberculous etiology. Dihydrostreptomycin therapy resulted in progressive healing of the lesions.—*Disseminated bone tuberculosis (so-called multiple cystic tuberculosis), G. H. Alexander & M. M. Mansuy, Radiology, December, 1950, 55: 839.*—(*W. J. Steininger*)

Endocardial Tuberculosis.—A case is presented of endocardial tuberculoma of the right auricle, associated with miliary spread and septic infarction of the brain and spleen in a man with preëxisting hypertensive heart disease (Authors' summary).—*Endocardial tuberculosis, E. Baron & D. W. Ritter, Ann. Int. Med., October, 1950, 33: 1023.*—(*T. H. Noehren*)

Bronchial Tuberculosis.—Among the female patients at a Belgian tuberculosis sanatorium, routine bronchoscopy revealed definite bronchial tuberculosis in 8.3 per cent of the patients admitted, suspected bronchial tuberculosis in 3.5 per cent, and bronchial fistulas from lymph nodes in 2 per cent. Isolated or primary bronchial lesion was diagnosed bronchoscopically in one-third of the patients with this disease before clinical or roentgenographic evidence of tuberculosis appeared elsewhere. Primary bronchial disease often was responsible for the expectoration of tubercle bacilli by apparently healthy persons with few symptoms or signs of disease; tomography occasionally revealed bronchial stenosis. The lesions sometimes healed during penicillin treatment, but more often spread by contiguous growth or bronchial dissemination. Pneumothorax was ill advised; in 7 cases of cicatricial bronchial stenosis and pulmonary collapse, there was evidence that therapeutic pneumothorax contributed to the complicating atelectasis. Bronchial tuberculosis secondary to parenchymal lesions usually had a grave prognosis even though the pulmonary disease appeared to heal. Pneumothorax was contraindicated but other forms of collapse therapy, cavity drainage, or resection were sometimes successful when combined with streptomycin, penicillin, and vitamin D therapy. Bronchoscopy was thought to be indicated in all tuberculous patients except those with hectic fever, progressive pulmonary lesions, or laryngeal tuberculosis. More or less serious complications followed in 12 (2 per cent) of 600 bronchoscopies and usually subsided after two or three days of penicillin therapy.—*Considérations sur la clinique, la pathogénie et le traitement de la tuberculose des bronches, A. Gyselen, P. Van de Calseyde, & M. Van de Maele, Acta tuberc. belg., August, 1950, 41: 229.*—(*A. T. Laird*)

Psychology of Tuberculous Children.—A study at Bellevue Hospital by Dr. Sara Dubo of children with tuberculosis has shown them to have specific psychologic reactions. Their behavior shows a diffuse motor activity, aggressive outbursts, and an inability to cooperate. They will accept collapse therapy measures but they resist rest in bed. They are anxious and deeply preoccupied. Regression is not notably common. The technique of precautionary measures is resented and this leads to defiance. Rorschach tests confirm the picture. Therapy should include a substitution for parents, recreation, group discussion, and identification with the adults.—*The child with tuberculosis, H. Bakwin, J. Pediat., December, 1950, 37: 936.*—(*W. H. Oatway, Jr.*)

Postpartum Pneumoperitoneum.—Of 39 tuberculous women delivered in 1947 and 1948, 36 were treated successfully with pneumoperitoneum immediately after delivery. The method usually has no contraindications and is well tolerated. The good results obtained demand its use following childbirth in tuberculous women not treated with pneumothorax. In 7 of these patients, tubal ligation, appendectomy, and pneumoperitoneum were performed without mishap. Pneumoperitoneum fillings should be rather large (approximately three liters) in order to secure an adequate high pressure. Tubal ligation is advised when a parturient tuberculous woman has already had 3 pregnancies and there is doubt as to the efficiency of the treatment she may

receive in the future.—*Pneumoperitônio imediato ao parto da tuberculosa, A. Vieira & J. Martins Sobrinho, Clín. Tisiol., January-March, 1950, 5: 111.*—(*A. A. Moll*)

Segmental Collapse in Pneumothorax.—Tuberculosis is essentially a segmental and subsegmental pathologic process. If damage in the branch bronchus or bronchi is accepted as an inevitable concomitant of the disease, it is but a short step to understand the mechanics of segmental or lobular collapse. In a pneumothorax where adhesions are absent, the most perfect form of selective collapse may be seen as shown by illustrative cases. This is first noted very early on the roentgenogram as a local condensation of the diseased area with a "dipping in" of the pleura, producing in many instances a scalloped effect. The collapsed area may retract toward the hilus to such an extent as to be difficult, finally, to recognize as a segment. Occasionally it may assume a rounded appearance and be indistinguishable from a round focus. In some cases there has been a changing evanescent quality to the segmental atelectasis with appearance and disappearance of the segmental selective collapse. Regardless of the factors of elasticity, neurovascular phenomena, reflex mechanisms, and others, it would appear that the major etiology of selective collapse rests upon bronchial obstruction, especially of the finer branches.—*Segmental collapse in therapeutic pneumothorax, A. Hurst & T. Millner, Radiology, August, 1950, 55: 228.*—(*W. J. Steininger*)

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Patterns of Pulmonary Fibrosis.—The lack of correlation between subjective and objective clinical findings of disturbed pulmonary function with the degree of fibrosis seen on the roentgenogram may, to a great extent, be resolved by an evaluation of the pattern of fibrosis rather than by the degree of fibrosis. Fibrosis of the lungs may occur in 5 distinct patterns: bronchial, interstitial, parenchymal, pleural, and vascular. These patterns often co-exist. The different patterns will, to a great extent, determine the type of functional disability. Bronchial fibrosis will produce functional changes associated with diffuse obstructive emphysema. Interstitial fibrosis will produce essentially diffusion disturbances. Vascular fibrosis will produce pulmonary hypertension. Pleural fibrosis will produce some degree of ventilatory disturbance, as will advanced degrees of parenchymal fibrosis. Diffuse interstitial fibrosis of the lung produces a distinct clinical pathologic syndrome. This entity is becoming more important and is more frequently recognized. It may possibly be related to some form of virus infection. Pulmonary fibrosis is most often only indirectly related to the development of pulmonary hypertension (Author's summary).—*Patterns of pulmonary fibrosis as related to pulmonary function, D. M. Spain, Ann. Int. Med., November, 1950, 33: 1150.*—(*T. H. Noehren*)

Granulomatous Pneumonitis.—An outbreak of an unusual illness occurred in a group of 12 men who had cleaned an abandoned tower containing a large quantity of wet pigeon excreta. The clinical manifestations appeared from five to fourteen days after exposure and varied from a mild, transitory grippe-like syndrome of a few days' duration to a more severe prostrating illness which lasted almost three weeks. Extensive laboratory studies failed to reveal a causative agent. The most striking feature was the pulmonary involvement revealed in roentgenograms of the chest. In each case the admission film obtained from five to seven days after the onset of symptoms showed innumerable finely nodular densities, diffusely and symmetrically distributed throughout the lung fields. The nodules appeared somewhat more concentrated in the central portions of the lung fields, varied from 1 to 3 mm. in diameter, and were ill defined and noncoalescent. The appearance was indistinguishable from that seen in miliary tuberculosis. On films obtained one week later, a slight increase in pulmonary involvement

was noted in 5 cases while no change was detected in the other 7. The subsequent roentgenologic course varied; in 7 cases the lesions became gradually less perceptible on each succeeding roentgenogram and ultimately faded completely. The clearing took place over a period varying from one to twelve months after onset, most cases showing complete disappearance of the miliary densities between the third and fifth months. In 4 of the remaining 5 cases, progressive but incomplete clearing occurred from the third week to the tenth month after onset. The process then appeared stationary during the remainder of the follow-up period. The fifth patient showed a similar pattern but died of coronary thrombosis at the end of five months, the last film showing a very faint diffuse pulmonary nodularity. No evidence of pulmonary calcification, emphysema, or cardiac enlargement appeared. In the cases in which complete regression of the lesion occurred, no abnormalities were apparent on the later films. Since small, granulomatous lesions were found in the lungs and tracheobronchial lymph nodes of the one patient who died, Feldman and Sabin designated this disease "diffuse miliary granulomatous pneumonitis." Three previous similar epidemics have been described. Cain found a similar disease in soldiers from an abandoned storm cellar; Washburn described "cave sickness" in men from a chalk mine; Idstrom and Rosenberg saw a similar epidemic in soldiers who were cleaning "dusty, abandoned homes, barns, chicken coops and outhouses." The similarity of roentgenographic changes and the similarity of exposure, symptoms, and laboratory findings suggest the possibility that all 4 outbreaks have the same or similar causes. Further investigation will be necessary to determine if these epidemics present a new disease entity.—*Roentgenologic aspects of diffuse miliary granulomatous pneumonitis of unknown etiology, B. Felson, G. F. Jones, & R. P. Ulrich, Am. J. Roentgenol., November, 1950, 64: 740.*—(*T. H. Noehren*)

Lung Changes during Recovery from Drowning.—A report is made of the roentgenographic and clinical findings in a patient who recovered after submersion in water for an unknown period. At thirty-six hours roentgenograms of the lungs showed mottled opacities with areas of confluence in the inner two-thirds of the lung fields in the pericardial regions. Subsequent roentgenograms demonstrated progressive clearing; at the end of three weeks the chest showed no significant abnormality. The abnormal radiographic shadows are believed to be due primarily to pulmonary edema. Small areas of segmental atelectasis may be an associated factor.—*Radiographic changes in the lungs during recovery from drowning, J. J. Romagosa, L. J. Menville, & J. T. Leckert, Radiology, October, 1950, 55: 517.*—(*W. J. Steininger*)

The Changing Nature of Pneumonia.—A change in the character of pneumonia in general occurs from time to time and depends chiefly on the presence or absence of certain epidemic forms of pneumonia, especially those caused by, or presumably caused by, viruses. The latter are apt to be widespread and to come and go in keeping with the natural waves of epidemic behavior. The 1941–1943 pandemic of the disease of which "viral" pneumonias were an integral part disturbed the statistical balance of cases at that time. Staphylococcal, streptococcal, Q fever pneumonia, and others are uncommon diseases but may occur in small localized outbreaks. In spite of impressions to the contrary, several studies indicate that the incidence of pneumococcal lobar pneumonia is remarkably constant, and was not significantly disturbed after 1939 either by the introduction of sulfonamides and antibiotics or by the transient pandemic of "viral" pneumonias. As in previous years, the character of lobar pneumonia is subject to variation from year to year in accordance with the predominance of pneumococci of different types. Modern therapy has caused a change in the clinical characteristics of lobar pneumonia. In adequately treated patients, the course of the disease is shortened and the death rate has been reduced. Insufficient therapy may modify the disease so

as to confuse diagnosis with various kinds of atypical pneumonia. The recognition of previously unknown forms of pneumonia, such as "viral" pneumonia, Q fever, ornithosis, and others, adds to diagnostic and therapeutic complexity. It is essential to establish etiologic diagnoses in all pneumonias, since different entities respond to different antibiotic agents and demand special epidemiologic management (Author's summary).—*The changing nature of pneumonia, H. A. Reimann, Ann. Int. Med., November, 1950, 33: 1246.*—(*T. H. Noehren*)

ACTH for Pneumonia.—The administration of adrenocorticotropic hormone (ACTH) to 3 patients with pneumococcal pneumonia and 2 with "viral" pneumonia was followed by prompt remission of the clinical symptoms associated with the acute illness but the remissions were not lasting in every case. In each patient, administration of the hormone was followed within twelve to twenty-four hours by diaphoresis, defervescence, and marked subjective improvement. These were preceded in some cases by a brief exacerbation during which the temperature, pulse, and respirations increased and general toxicity was intensified. In the pneumococcal pneumonias, pneumococci were abundantly present in the sputum after the patients had become afebrile and asymptomatic, and in one patient bacteremia was demonstrated twelve to thirty-six hours after the patient had become clinically well. Rusty sputum was first noted in that patient after he had become afebrile, and similar sputum was raised for five days after the apparent remission of the acute illness in the second case of pneumococcal pneumonia. One patient with pneumococcal pneumonia experienced an exacerbation of symptoms while receiving ACTH and remitted when the dose was increased. This patient had an extension of his pulmonary lesion and later developed empyema. One patient with viral pneumonia had a similar exacerbation of symptoms while receiving the hormone; prompt relief from all of the symptoms except cough resulted when the dose of ACTH was increased. Fever and malaise returned after ACTH was withdrawn. Eosinophilic leukocytes were uniformly absent in all of the cases during the illness and returned either after the dose of ACTH was reduced or, as in one case, when the patient developed tolerance to the administered dose of the hormone and "escaped" from its effects. Clearing of the pulmonary lesions may have been accelerated in one patient and delayed in another, but in the remaining 3 patients resolution of the pneumonic process seemed to have been neither accelerated nor delayed. Antipneumococcal antibodies and cold agglutinins appeared at the anticipated time. It is concluded that ACTH may in some instances induce profound changes in the clinical symptoms of patients with acute infections without demonstrably affecting the etiologic agent.—*Effects of adrenocorticotropic hormone in pneumonia: Clinical, bacteriological, and serological studies, E. H. Kass, S. H. Ingbar, & M. Finland, Ann. Int. Med., November, 1950, 33: 1081.*—(*T. H. Noehren*)

Auscultation at Nose and Mouth.—Physical examination of infants and children may be augmented by listening to the breath sounds with a stethescope held in front of the nose and mouth. Obstructions, irregularities, rales, and other abnormalities may be noted without disturbing or undressing the patient. It is valuable when the patient is in a respirator.—*Prenasal and preoral auscultation, J. L. Wilson, J. Pediat., November, 1950, 37: 759.*—(*W. H. Oatway, Jr.*)

Bronchoscopic Topography.—The bronchial divisions were studied during several hundred bronchoscopies at the Laënnec Hospital in Paris. The orifice of the right upper lobe bronchus had 2, 3, and 4 openings. In 62.5 per cent of the cases there was an orifice with 3 visible openings which represented the apical, anterior, and posterior divisions. The external branch did not originate from the stem bronchus but from the anterior or posterior division, or from both. In 23.5 per cent of the cases there was an orifice of the right upper lobe bronchus with 2 openings, a common

trunk uniting the apical to the anterior or posterior branch. The external branch originated from the anterior or posterior branch, or from both. An orifice with 4 openings representing a branch for each segment of the right upper lobe was found in 14 per cent of the cases. This constellation facilitated the catheterization of each bronchial division. No abnormal topography of the right middle lobe bronchus was encountered in this series. Its anterior and external divisions were bronchoscopically visible in 50 per cent of the cases. The divisions of the right lower lobe bronchus were classified into the apical, anterior, external, posterior, and internal branches. The apical and external branches were easy to identify and showed almost constant topography; they were fairly accessible for catheterization. The right lower lobe bronchus had visible openings of only the apical and internal branches in 50 per cent of the cases. Three openings were found in 42 per cent of cases, 4 openings in 6.6 per cent, and one visible orifice in 1.4 per cent of cases. The left upper lobe bronchus in 61 per cent of the cases showed only 2 openings, one of them being the orifice of the lingular branch. In 31.7 per cent, as well as the orifice of the lingular branch there were 2 other orifices, probably those of the anterior and posterior branches. In 7.3 per cent, 4 openings were visualized, representing the lingular, anterior, posterior, and apical branches. The left lower lobe bronchus showed openings in 69 per cent of cases, 4 openings in 28.6 per cent, and 5 openings in 2.4 per cent. The orifice of the apical branch was always present.—*Constatations sur la topographie bronchoscopique et sur le cathétérisme des orifices bronchiques, G. Arnaud & J. Ionnou, Semaine d. hop. Paris, August 18, 1950: 2023.*—(*V. Leites*)

Spontaneous Pneumothorax.—In an 18-month period at the Philadelphia Naval Hospital, the diagnosis of spontaneous pneumothorax was established in 26 male patients; 25 were white and one was a Negro. All were previously in good health with the exception of one patient with advanced rheumatoid spondylitis and one with known active pulmonary tuberculosis. Six of the 26 had had previous episodes of collapse, the greatest number in any one patient being 4. The extent of collapse varied from 15 to 100 per cent, the majority exceeding 50 per cent. The time required for re-expansion was quite variable, bearing no direct relationship to the degree of collapse. For example, one patient with 100 per cent collapse required 13 days, while another with 20 per cent required 21 days for complete re-expansion. In 1945, when the Navy and Marine Corps had a peak average strength of 3,673,855, the diagnosis of pneumothorax was made 651 times; 65 (10 per cent) were readmissions. More than 12 per cent were invalidated from the service, and 6 died. —*Spontaneous pneumothorax, R. K. Moxon, U. S. Armed Forces M. J., October,, 1950, 1: 1157.*—(*T. H. Noehren*)

Fatal Spontaneous Hemopneumothorax.—Only 5 cases of fatal spontaneous hemopneumothorax have been reported in Brazil; one more is added. The patient, a 40-year-old man, who had done very heavy work for several days developed suddenly a most severe pain in the left side of the chest. A clinical diagnosis of a spontaneous tension pneumothorax was confirmed roentgenographically. All treatment proved ineffectual. The patient was found afterwards to be a hemophiliac. Autopsy disclosed the left hemithorax to be completely filled with blood except for three juxtahilar pleural gas bubbles. There was a ruptured blood vessel on the internal surface of the lung.—*Hemopneumotórax espontâneo mortal, Granadeiro Neto, Rev. brasil. med., June, 1950, 7: 418.*—(*A. A. Moll*)

Pneumothorax in Asthma.—Spontaneous pneumothorax in patients with asthma may be more common than is generally recognized. A sudden critical increase in dyspnea and cyanosis or the onset of pain confined to one side of the chest should direct inquiry in this direction. Pneumothorax, interstitial emphysema, or both, can be fatal for asthmatic patients. Of 5 cases presented 2 were fatal.

In both fatal cases there was extensive bronchiolar plugging by mucus, and measures to remove mucus are of greatest importance. Hydration, iodides, relief of bronchiolar spasm, and, especially, prompt bronchoscopic aspiration are probably of as great importance as the pressure effects of interstitial emphysema or pneumothorax.—*Pneumothorax and interstitial emphysema in asthma, H. S. Mitchell & H. L. Bacal, Canad. M. A. J., November, 1950, 63: 467.*—(*T. H. Noehren*)

Simulated Hydropneumothorax.—A patient with an acute pulmonary infection of the right lower lobe presented on roentgenographic examination the appearance of a hydropneumothorax. A congenital anomaly was suspected and a barium meal demonstrated that the appearance of hydropneumothorax was in reality produced by a right-sided stomach with eventration of the right diaphragm. There was no evidence of transposition of other organs (Author's summary).—*Right-sided stomach associated with eventration of the diaphragm simulating hydropneumothorax, H. R. Nayer, Am. J. Roentgenol., July, 1950, 64: 50.*—(*T. H. Noehren*)

Traumatic Pulmonary Collapse.—A sudden massive collapse of the left lung occurred in one patient five days after a serious automobile accident. The patient was fully conscious, with normal cough reflexes. The collapse resolved in two days leaving only a segmental area of atelectasis. It is very unlikely that the collapse in this case was due to a mucous plug obstructing the left main bronchus; the sudden collapse of a whole lung may be explained rather by an active contraction of the lung. The mucous plug or a foreign body in the bronchus may act as a factor eliciting a reflex mechanism which determines the active contraction of the lung.—*Der posttraumatische Lungenkollaps, V. Knoll, Fortschr. a. d. Geb. d. Rontgenstrahlen, October, 1949, 71: 931.*—(*L. Molnar*)

Unilateral Pulmonary Stasis.—A transitory stasis in one lung is observed when the pulmonary veins are kinked by a considerable shift of the mediastinum causing a partial interruption in the venous flow. This occurs in cases of pneumothorax, diaphragmatic hernia, relaxation of the diaphragm. In such cases the accentuation of the vascular markings in the contralateral lung is more evident in the expiratory phase. A permanent stasis in one lung is a rare occurrence and its etiology is obscure. One case of right-sided stasis was observed as an incidental finding in an individual showing clinical signs of bronchitis. After ruling out all other possible factors, the cause of the stasis was attributed to adhesions following mediastinal pleurisy, with consequent narrowing of the lumen of the pulmonary veins. However, in view of the rarity of this condition after mediastinal pleurisy, this explanation can be admitted only as an exception.—*Uber einseitige Lungenstauung, R. Haubrich. Fortschr. a. d. Geb. d. Rontgenstrahlen, August, 1949, 71: 511.*—(*L. Molnar*)

Pulmonary Arterial Aneurysm.—A case of left pulmonary arterial aneurysm, probably due to arteriosclerosis, was diagnosed by angiocardiography. Angiocardiography provides the only accurate means for diagnosing a pulmonary arterial aneurysm before operation or autopsy. This procedure will establish the vascular nature of the lesion, identify it with the pulmonary artery, and demonstrate its aneurysmal character as fusiform or saccular. Other cardiovascular lesions or anomalies can be found if present. The etiology of the aneurysm must still be determined at operation or post mortem, although clinical studies may be suggestive.—*Aneurysm of the pulmonary artery: A case diagnosed by angiocardiography, C. A. Priviteri & B. B. Gay, Radiology, August, 1950, 55: 247.*—(*W. J. Steininger*)

Subdiaphragmatic Abscess.—In studying a patient suspected of having a subdiaphragmatic abscess, fluoroscopic and radiologic examination of the chest and abdomen should be performed in both the recumbent and erect positions. One of the earliest evidences of subphrenic abscess is restricted mobility of the

involved hemidiaphragm. Elevation and fixation of the hemidiaphragm occur later, being more prominent and more readily evident on the right. As a result of lymphatic extension, a basilar pleurisy with effusion occurs in nearly all suprahepatic abscesses. Lobular atelectasis of the lower lobe usually accompanies the early changes, followed by a lobular pneumonia which tends to involve the inferior segment of the lower lobe following the contour of the hemidiaphragm. These intrathoracic manifestations are extremely significant and may dominate the clinical features, particularly in those abscesses involving the suprahepatic spaces; in fact, they may be the first suggestion of the presence of subdiaphragmatic abscess. In about 25 per cent of cases, the abscess itself may be visualized as an air-fluid accumulation in the subdiaphragmatic space, the air being due to communication with a hollow viscus. A right subphrenic abscess displaces the liver downward. In the presence of abscess on the left side, the stomach is displaced inferiorly and may be displaced medially and anteriorly. When the abscess is present in the right infrahepatic space, there is persistent dilatation of the stomach and proximal duodenum.—*Roentgen diagnosis of subdiaphragmatic abscess, P. S. Friedman, Radiology, July, 1950, 55: 36.*—(*W. J. Steininger*)

Congenital Diaphragmatic Defect.—A congenital diaphragmatic hernia was found in a newborn infant, the autopsy disclosing a large defect posterolaterally in the left diaphragm. In the left hemithorax was found all of the intestinal tract from the duodenum to the mid-transverse colon as well as the spleen, the pancreas, and the collapsed left lung. The mediastinum was pushed far to the right, with resultant collapse of the right lung. Gradual filling of the bowel with gas during the first few hours of life caused progressive dyspnea, tachypnea, and cyanosis. Death was caused by a combination of anoxia with cardiac embarrassment by the anoxia and the mechanical pressure exerted by the distended bowel. Dyspnea, cyanosis, and general physical distress occurring together in a newborn infant, sometimes accompanied by vomiting, are suggestive of diaphragmatic defects and the presence of abdominal viscera in the thorax. Physical examination is confirmatory and fluoroscopy and roentgenograms are diagnostic. Surgical repair of these defects is quite successful and should be done early.—*Congenital defect in the diaphragm, F. H. Decker & J. C. Fash, Radiology, September, 1950, 55 :415.*—(*W. J. Steininger*)

Diaphragmatic Omental Hernia.—Developmental errors involving the diaphragm and predisposing to hernia are of 3 types: (*1*) faulty relationship of the structures passing through the diaphragm (aorta, vena cava, and esophagus) to their corresponding orifice; (*2*) a defect in the diaphragmatic muscle fibers near the sternum, at the so-called foramen of Morgagni; (*3*) absence of atresia of the posterior or segment of one or both hemidiaphragms due to underdevelopment of the pleuroperitoneal membranes. Among diaphragmatic hernias, those through the foramen of Morgagni are least common and in this group are the omental hernias. As shown in 4 cases, these hernias may be mistaken on the roentgenograms for cysts or other pathologic processes of the right lung or for liver cysts. The following radiographic features are characteristic: (*1*) a dense shadow forming a semicircle in contact with the right diaphragm at a point where the latter seems to be interrupted, forming two lateral arcs; (*2*) immobility of the diaphragm, sometimes with a paradoxical movement of the shadow; (*3*) displacement of the duodenum to the upper right abdomen and insinuation of the right colon near the pathologic shadow. Diagnostic pneumoperitoneum makes possible a definite diagnosis. If the hernia is a true one, air will accumulate around the pathologic shadow; if it is a pseudo-hernia, without a peritoneal sac, a pneumothorax will develop.—*Pseudo-cystic shadows of the right pulmonary base due to diaphragmatic omental hernia, F. G. Capurro & M. A. Bellini, Radiology, September, 1950, 55: 410.*—(*W. J. Steininger*)

Traumatic Diaphragmatic Hernia.—Diaphragmatic hernias are encountered with increasing frequency in modern roentgenologic practice. Esophageal hiatal hernia is by far the most common variety. The nonhiatal hernias are most frequently caused by direct trauma with actual laceration of the diaphragm, although some occur through pre-existing congenital weak spots, the foramen of Bochdalek or Morgagni, or as a result of absence of portions of the leaf. Diaphragmatic hernias are often asymptomatic and may go undiagnosed for a considerable period. The nonhiatal hernias frequently masquerade as other pulmonary or pleural lesions in the basal portions of the left lung field. Often a large portion of the gastrointestinal tract is involved, quite frequently the spleen, and at times the pancreas and even the left kidney. The frequent occurrence on the right is probably due to the protection afforded by the liver. Pure omental hernias present themselves as well-marginated, spherical masses just above the diaphragm. Whenever a deformity of the left diaphragm is demonstrated in the chest film, or there is an unexplained density in the left base partially obscuring the diaphragm without other evidences of pulmonary infection, the possibility of diaphragmatic hernia should be considered. —*Traumatic and related types of diaphragmatic hernia, F. Isaac, F. B. Wilkins, & J. Weinberg, Radiology, October, 1950, 55: 527.*—(*W. J. Steininger*)

Real Ectopia in Diaphragmatic Hernia.—Thoracic ectopia of the right kidney was observed in an elderly woman. It presented itself, like other congenital hernias, in the posterior medial portion of the diaphragm in the region of the trigonum lumbocostale or "foramen of Bochdalek." The content of the hernia was identified as kidney by intravenous urography. There were no clinical signs or symptoms referable to the anomaly. This seems to be the first instance in which the diagnosis was made during life (Authors' summary).—*High renal ectopia and congenital diaphragmatic hernia, F. C. Fleischner, S. A. Robins, & M. Abrams, Radiology, July, 1950, 55: 24.*—(*W. J. Steininger*)

Subdiaphragmatic Intestine.—Interposition of the small intestine between the liver and diaphragm was found roentgenographically in a patient. It is important not to mistake hepato-diaphragmatic interposition for a perforated abdominal viscus or subphrenic abscess, and to realize that it can coexist with either of these conditions. It may also represent an internal hernia of small intestine. Large and small intestine interposition can be differentiated positively only by a barium enema. It is probable that most cases of interposition are asymptomatic per se.—*Hepato-diaphragmatic interposition of the small intestine, J. F. Linsman & J. I. Chalek, Radiology, May, 1950, 54: 726.*—(*W. J. Steininger*)

Sputum Cytology.—In a group of 588 cases of miscellaneous chest diseases, a routine cytologic examination of sputum or bronchial secretions was carried out; 147 cases of proved or suspected bronchogenic carcinoma occurred. Of these 147 cases, 100 (68 per cent) were detected by cytologic examination. No known false positive diagnoses occurred in this series. Of 93 patients with bronchogenic carcinoma who underwent bronchoscopic examination, a positive biopsy was obtained in 38 (41 per cent). In this same group, cytologic studies were positive in 65 cases (70 per cent). In 5 cases, the roentgenograms suggested tuberculosis, but the presence of exfoliated cancer cells in the sputum provided convincing evidence that the lesions in question were neoplastic. Pancoast's tumor was diagnosed in 8 cases, 5 of which were preoperatively determined by the presence of carcinoma cells in sputum or bronchial washings. Bronchoscopic examination was carried out in only 2 of these cases and in both was negative. Three additional cases of alveolar cell carcinoma are included in this series. In one case the diagnosis was first indicated by cytologic findings in the sputum; in the other 2, unusual cells were found but were not sufficiently atypical to warrant a definite cytologic diagnosis.—*Cytology of sputum and bronchial secretions: Studies on 588 patients with miscellaneous pulmonary lesions, L. B. Woolner & J. R. McDonald,*

Ann. Int. Med., November, 1950, 33: 1164.—(T. H. Noehren)

Bronchial Carcinoma as Pancoast Tumor.—The superior pulmonary sulcus tumor may originate in any section of the lung or of the chest. Of 63 cases examined histologically, 49 of them confirmed by post-mortem examination, about half showed highly differentiated types of carcinoma and about one-third were adenocarcinomas. Bronchial carcinoma shows a very similar incidence of histologic types. Other characteristics of Pancoast tumors, similar to those of bronchial carcinoma, are the prevalence in males, age, tendency to local invasion, tendency to necrosis, type of metastasis, and poor response to rontgenographic treatment. The hypothesis is advanced that the peripheral growth is due to pre-existing pleural adhesions which would direct the development of the tumor. Apical adhesions were found in 20 cases on the post-mortem examination of 49 cases of Pancoast tumor. Three cases are described in which the diagnosis was made on hard penetrating films showing the destruction of ribs or vertebrae.—*Der Pancoast-tomor als eine Ausbrecherform des Bronchuskrebses, H. Eschbach, Fortschr. a. d. Geb. d. Rontgenstrahlen, October, 1949, 71: 927.*—*(L. Molnar)*

Neoplastic Effusions.—Cytologic examinations and lactic acid and glucuronidase determinations were performed with 169 effusion fluids taken from 56 patients. It appears that neoplastic effusions are frequently but not always rich in glucuronidase, lactic acid, and cancer cells and that these components are absent (cancer cells) or low (glucuronidase, lactic acid) in non-neoplastic effusions and neoplastic transudates. In the course of the disease all 3, or any one, of these indices may change in either direction. High glucuronidase and elevated lactic-acid levels can occur only if there is reasonably intimate contact between a tumor and the fluid studied. Cells may or may not desquamate into such fluids and the extent of desquamation may vary. Positive cytologic findings are not always accompanied by an elevated concentration of lactic acid and glucuronidase and elevation of the latter components is not invariably accompanied by the presence of detectable tumor cells. In terms of clinical experience, the elevation of both glucuronidase and lactic acid appears to be of itself diagnostic for the presence of cancer; whereas the absence of these findings has no significance for the ruling out of cancer.—*—Studies on effusions: I. Glucuronidase and lactic acid in neoplastic effusions of pleura and peritoneum, W. H. Fishman, R. I. Markus, O. C. Page, P. H. Pfeiffer, & F. Homburger, Am. J. M. Sc., July, 1950, 220: 55.*—*(W. J. Steininger)*

Metastases from Salivary Gland Cancer.—Skeletal and intrathoracic metastases from 49 cases of cancer of the major salivary glands have been studied roentgenographically. Among 33 cases with metastasis to the bones there were 21 with a solitary metastasis and 12 with multiple lesions. The location was as follows: mandible in 20, spine in 8, pelvis in 6, skull in 5, ribs in 3, femur in 3, scapula in one, and humerus in one. The metastases in bone, usually confined to the medulla, were classifiable into 3 general types on the basis of their roentgenographic appearance. (*1*) The "patchy" type showed irregular motheaten areas of bone destruction. (*2*) The "lytic" type was characterized by large, purely destructive defects. (*3*) The "erosive" type presented margins with a wavy, scalloped configuration. Among the 28 cases with intrathoracic metastases, mediastinal involvement occurred once, a pleural reaction was observed in 7 instances, and there were 23 cases of pulmonary metastasis. The majority of the parenchymal lesions were multiple and nodular, as a rule diffusely scattered in the lungs. No instance of calcification or excavation was discovered. In 5 cases the parenchymal lesions were miliary in type with innumerable small discrete circular densities diffusely scattered throughout each lung. In no case was a lymphatic form of metastasis seen.—*A roentgen study of skeletal and intrathoracic metastases from salivary gland cancer,*

D. Wilner, Radiology, December, 1950, 55: 801.—(W. J. Steininger)

Pulmonary Adenomatosis.—Benign pulmonary adenomatosis is a rare pulmonary disease of unknown etiology, characterized by a remarkable proliferation of alveolar lining cells throughout large areas of the lungs, by an absence of invasive characteristics, and by an absence of regional or distant metastases. The diagnosis of pulmonary adenomatosis should not be difficult if the case presents the usual clinical and roentgenographic features. If the patient complains of progressive dyspnea, cough productive of abundant amounts of mucoid sputum, and weight loss, and if the roentgenogram reveals extensive discrete and confluent nodular densities in the lung fields without hilar or mediastinal adenopathy, the provisional diagnosis should be pulmonary adenomatosis. Bronchoscopy reveals tremendous quantities of mucoid sputum. Exfoliative cytology studies have not been diagnostic to date. Aspiration biopsy of the lung would seem to be the best method of confirming the diagnosis. The treatment of pulmonary adenomatosis is purely symptomatic; none of the 4 cases reported here survived. Lobectomy is probably indicated if the disease is localized in one lobe.—*Pulmonary adenomatosis. A report of four cases, J. C. King & D. S. Carroll, Radiology, November, 1950, 55: 669.*—(*W. J. Steininger*)

Pulmonary Adenomatosis.—The pathologic picture of pulmonary adenomatosis is variable. In its simplest form, the disease resembles a benign growth in all respects, dyspnea and cough productive of large amounts of watery sputum are significant findings, and death results from interference with the normal functions of the lungs and from complicating infection. In other cases the basic histologic picture is the same, but study of surgical or autopsy specimens shows areas of frank carcinomatous changes and even distant metastases. The most common roentgenographic appearance is that of single or multiple areas of homogeneous density resembling pneumonic consolidation. Atelectasis is not apparent, and there is no evidence of mediastinal lymphadenopathy or pleural involvement. Serial observation over a period usually of months show a slow progression of the disease until finally little normally aerated lung remains. Less frequently a nodular type of the disease is found resembling metastatic carcinoma roentgenographically. Cytologic study of the sputum may give a clue to the diagnosis in some cases. No method of treatment has been successful in curing the disease. Lobectomy or pneumonectomy may give worthwhile palliation, but all of the evidence indicates that the tumor is of multicentric origin and that, even when it is apparently localized to one lobe, other foci of neoplastic growth probably exist.—*Pulmonary adenomatosis: Further roentgen observations, L. W. Paul & J. H. Juhl, Radiology, November, 1950, 55: 681.*—(*W. J. Steininger*)

Hamartoma.—In the past six years, 17 hamartomas of the lung have been removed surgically at the Mayo Clinic, and the diagnosis has been made subsequently by microscopic examination of the tissue. Thirteen of the tumors were found on the right and 4 on the left side; 7 lay close to fissures or were subpleural. In 15 of the cases the tumors contained cartilage and some of the other characteristic tissues. In 2 cases diagnosis even by tissue examination was difficult. The ratio of men to women was nearly 2 to 1; the average age was approximately 47 years, and the range in age from 21 to 62 years. Symptoms were not helpful in diagnosis. In only 5 cases could a possibility or probability of the diagnosis of hamartoma be based on roentgenographic grounds. Bronschoscopy would not have aided the diagnosis nor would cytologic examination of sputum have excluded the possibility of carcinoma. Study of the 17 cases did not disclose a diagnostic alternative to exploratory thoracotomy. Experience in these cases accorded generally with that of others, except that in this series the roentgenographic findings were less characteristic than some other investigators have considered them to be.—*Hamartoma of the lung: The improbability of preoperative*

diagnosis, W. E. Lemon & C. A. Good, Radiology, November, 1950, 55: 692.—(W. J. Steininger)

Pulmonary Air Meniscus.—The pulmonary air meniscus is a radiologic sign consisting of a crescent-shaped air shadow surmounting a rounded area of density in the lung parenchyma. This phenomenon has been observed in a limited number of pulmonary disorders, notably hydatid disease, pulmonary cysts, and abscesses. In 2 cases the cause of this sign was determined. In the first, development was studied by serial roentgenograms; the rounded density was inspissated material contained in a lung abscess cavity. In the second instance a ball of fungal mycelia produced a rounded mass in a bronchogenic cyst. In a third case, an ovoid aggregate of fungus was likewise believed to be present in a pre-existing bronchiectatic cavity.—*The pulmonary air meniscus, H. S. Weens & E. A. Thompson, Radiology, May, 1950, 54: 700.—(W. J. Steininger)*

Linear Shadows in Lung.—Horizontal linear densities in the right upper lung field, regarded in the past as sequelae to interlobar pleurisy, are often due to the sclerosis or atelectasis of a pulmonary segment, accompanied by bronchiectasis. On closer study, these apparently linear shadows appear broader than that caused by the thickened interlobar pleura and may contain such structures as calcifications, blood vessels or dilated bronchi. An accurate study of the chest films completed by tomography revealed the true nature of these shadows in 4 cases. Their etiology is often tuberculous but similar shadows may be observed as sequelae to other pulmonary processes. The practical significance of the study of these densities consists in the fact that they may represent an active tuberculous bronchitis.—*Über radiäre Streifenschatten im rechten Lungenoberfeld, C. Esser, Fortschr. a. d. Geb. d. Rontgenstrahlen, June, 1949, 71: 205.—(L. Molnar)*

Roentgenologic Findings in Grippe.—Chest films of 30 patients hospitalized during an epidemic in Wurttemberg during the period from November, 1948 to March, 1949 showed mainly 2 patterns: (*1*) light densities in the hilar region, or connected to it with either a predominantly streaky character or of a more homogeneous appearance; (*2*) cloudy and partially patchy densities with no apparent connection to the hilum. In many cases the findings are not so clear-cut, and it is difficult to refer them to either one of the above patterns. No attempt was made to relate the roentgenologic appearance of the lesions to the etiology, but it is believed such studies on a large scale would be fruitful.—*Über Lungen-verschattungen bei Grippe, R. Glauner & E. Freeb, Fortschr. a. d. Geb. d. Roentgenstrahlen, January, 1950, 72: 282.—(L. Molnar)*

Localization of Intrathoracic Lesions.—A method of localizing intrathoracic lesions from the postero-anterior roentgenogram of the chest is based upon the premise that an intrathoracic lesion in anatomic contact with a border of the heart or aorta will obliterate that border. Such a lesion not contiguous with a border of the heart or aorta will not obliterate the border. The term "silhouette sign" indicates obliteration of a part of the cardiovascular silhouette by adjacent diseases. The following applications appear to be justified: (*1*) A shadow which causes obliteration of part or all of the heart border is anterior in location and lies in the middle lung lobe, lingula, anterior mediastinum, lower end of the major interlobar fissure, or anterior portion of the pleural cavity. (*2*) A density which overlaps the heart border, but does not obliterate it, is posterior in location and lies either in a lower lobe, the posterior mediastinum, or the posterior portion of the pleural cavity. (*3*) A radiopacity which obliterates the right border of the ascending aorta is anteriorly located and is situated either in the anterior segment of the right upper lobe, the middle lobe, the right anterior mediastinum, or the anterior portion of the right pleural cavity. (*4*) A density which overlies but does not obliterate the right border of the ascending aorta lies posteriorly and is located either in the superior segment of the

right lower lobe, posterior segment of the right upper lobe, posterior mediastinum, or posterior portion of the pleural cavity. (5) An opacity which obliterates the left border of the aortic knob lies in the apical-posterior segment of the left upper lobe or in the mediastinum adjacent to this segment. (6) A shadow which overlaps but does not obliterate the aortic knob is anterior or markedly posterior and lies either in the anterior segment of the left upper lobe, superior segment of the left lower lobe, or in the anterior or posterior portion of the superior mediastinum or pleural cavity. This method was tested in 84 cases, and accurate localization was obtained in nearly every instance.—*Localization of intrathoracic lesions by means of the postero-anterior roentgenogram: The silhouette sign, B. Felson & H. Felson, Radiology, September, 1950, 55: 363.—(W. J. Steininger)*

Angiocardiography in Congenital Heart Disease.—The angiocardiographic findings in 21 instances of tricuspid stenosis or atresia have been received. The cases were divided on the basis of "visualization" and "nonvisualization" of the right ventricle by angiocardiography and further divided according to presence or absence of transposition of the great vessels. The presence of an interatrial septal defect was inferred in all instances and directly demonstrated in 3. The three principal features of the anomaly which are demonstrated by angiocardiography include: (1) the existence of an interauricular septal defect; (2) nonvisualization of the right ventricle or visualization of a diminutive chamber; and (3) the presence of a large left ventricle. In the 19 cases with a clinical impression of tricuspid stenosis or atresia, the significant information elicited by antiocardiography may be summarized as: (1) clarification of impressions reached by other studies; (2) evaluation of the size of the interauricular septal defect; and (3) demonstration of anomalies of the great vessels, some of which had been unsuspected. Tricuspid stenosis or atresia with hypoplastic ventricle is a condition which can be satisfactorily demonstrated by angiocardiography. The risk of the procedure is such that it should not be used indiscriminately in all instances of congenital cyanotic heart disease but only after the careful selection of cases in which other clinical methods have failed to elicit the desired information.—*Angiocardiography in congenital heart disease of cyanotic type: II. Observations on tricuspid stenosis or atresia with hypoplasia of the right ventricle, R. N. Cooley, R. D. Sloan, C. R. Hanlon, & H. T. Bahnson, Radiology, June, 1950, 54: 848.—(W. J. Steininger)*

Electrokymography in Constrictive Pericarditis.—A plateau-like appearance of the diastolic portion of the ventricular electrokymographic tracing is described as characteristic of constrictive pericarditis under the proper conditions, although there are other causes of this appearance. Four cases of constrictive pericarditis are reported in which electrokymographic tracings of this type were obtained. In another patient with a pleuropericardial adhesion, electrokymograms obtained near the adhesion showed the same appearance. Recognition of pericardial constriction in patients in whom it is not suspected is suggested as one of the benefits of using electrokymography routinely in addition to fluoroscopy of patients with cardiac disease (Authors' summary).—*Electrokymographic observations in constrictive pericarditis, F. G. Gillick & W. F. Reynolds, Radiology, July, 1950, 55: 77.—(W. J. Steininger)*

Roentgen Kymography.—This procedure was devised originally for the study of cardiac disorders and its most important applications are still in this sphere, particularly in pericarditis and coronary disease. It is also useful in the differentiation of a bronchogenic neoplasm from an enlarged pulmonary artery. In the latter, typical waves are seen. Also, the method is of value in differentiating a mediastinal tumor from an aortic aneurysm or infolded aorta. In the case of tumor, the kymogram will show a normal aortic pulsation independent of abnormal shadows. This is not true of aortic aneurysm. The method is of no help in

the study of pulmonary cavities.—*The place of X-ray kymography in intrathoracic disease, G. Simon, Brit. J. Tuberc., October, 1950, 44: 93.*—(*A. G. Cohen*)

ANTIMICROBIAL THERAPY

Treatment with Streptomycin and PAS.—Patients between the ages of fifteen and thirty with recent acute, progressive, bacteriologically proved, bilateral pulmonary tuberculosis unsuitable for collapse therapy were included in a study by the Medical Research Council in cooperation with the British Tuberculosis Association Research Committee. The 166 patients were divided into 3 groups: (*1*) 59 were treated with 20 gm. of *p*-aminosalicylic acid (PAS) in the form of sodium salt given daily in 4 doses; (*2*) 54 received 1 gm. of streptomycin daily in one intramuscular injection; (*3*) 53 were given both PAS and streptomycin in these dosages. Chemotherapy combined with bed rest was continued for three months and was followed by one month's observation on bed rest alone. Toxic reactions were few. Of the patients on streptomycin, 12 per cent complained of transient giddiness; in only one instance was it severe. Three patients on PAS alone and 4 patients on combined therapy developed skin eruptions. Gastrointestinal symptoms of nausea or diarrhea with or without vomiting developed in 58 per cent of the PAS group and in 51 per cent of the combined group but were not sufficiently severe to warrant cessation of therapy. At the end of six months there were 8 deaths: the mortality differences in the 3 groups were not statistically significant. The fatality rate of 3 per cent in the PAS group was considerably lower than that of 27 per cent in a control group of similar cases treated in an earlier study on bed rest alone. In all 3 groups, the majority of patients had improved at the end of six months. Improvement was seen in 56 per cent of the patients in the PAS group, in 74 per cent of the streptomycin group, and in 87 per cent of the combined group. In this last group, the degree of improvement was most marked. Of the PAS-treated group, 34 per cent showed no material roentgenographic change as compared with 6 per cent in both the streptomycin and combined groups. In all groups the poorest results were seen in patients who had gross cavitation and were febrile at the start of treatment. Improvement was noted more frequently among women than men. Sputum conversion consistently occurred more often in the combined than in the PAS or streptomycin groups, not only in the proportion of specimens giving negative cultures, but also in the proportion of specimens positive on culture alone. Following termination of treatment, 27 per cent of the patients in the combined group had negative sputum as compared with 13 per cent of the streptomycin patients and 11 per cent of the PAS patients. A considerable difference in the emergence of drug-resistant strains was noted. Of the patients receiving streptomycin alone 70 per cent developed significant bacterial resistance to this agent as compared with 9 per cent in the group receiving combined therapy. At the end of six months, 89 per cent of the patients in the latter group producing positive cultures had completely sensitive strains as compared with only 21 per cent in the streptomycin group. PAS resistance was observed in several of the patients receiving PAS alone. The disease followed a less favorable course in patients with streptomycin-resistant strains, with more clinical relapses. The combination of PAS with streptomycin not only renders effective the administration of the drug for longer periods, but probably also permits repeated effective courses. The argument that the use of streptomycin may cause drug resistance and thus prejudice the eventual prognosis is now less valid and the extensive use of chemotherapy to early or small lesions is worth investigation.—*Treatment of pulmonary tuberculosis with streptomycin and para-aminosalicylic acid, a Medical Research Council investigation, Brit. M. J., November 11, 1950, No. 4688: 1073.*—(*E. A. Riley*)

PAS-resistant Organisms.—*p*-Aminosalicylic acid (PAS) sensitivity studies were performed at Fitzsimons Army Hospital on one or more cultures from 303 patients who had

not received the drug. Minor variations in sensitivity were observed with different strains of *M. tuberculosis* and with different cultures from the same patient, but cultures from all 303 patients were sensitive to the drug. *In vitro* resistance to 10 or more γ of PAS per ml. developed in cultures from 19 of 37 tuberculous patients who received from 7.2 to 14.4 gm. of the drug daily for 120 consecutive days.—*Para-aminosalicyclic and resistant Mycobacterium tuberculosis, W. E. Dye & E. H. Gogley, U. S. Armed Forces M. J., October, 1950, 1: 1157.*—(*T. H. Noehren*)

Synergism of Tuberculin and Streptomycin.—Bettega treated 41 patients with tuberculosis in various stages, the majority having advanced lesions. Most of them received streptomycin and a few, PAS. Repeated tuberculin tests were carried out throughout the treatment. Results were good in 27 cases; poor in 4; arrest occurred in 7, recovery in one, and death in one. In interpreting this favorable outcome, Mazzini Bueno suggests that the repeated use of tuberculin at short intervals helped considerably by causing focal disintegration and setting loose bacillary masses on which the antibiotics acted more promptly and effectively.—*Conceitos novos no tratamento da tuberculose pelos antibióticos mais ação da tuberculina, Mazzini Bueno & J. L. Bettega, Clín. Tisiol., January-March, 1950, 4: 111.*—(*A. A. Moll*)

TB 1 for Pulmonary Tuberculosis.—The long-range results were studied in 12 cases treated with TB 1 for a period of six to eighteen months. In 6 cases there was either no manifest therapeutic effect or it could not be evaluated because the chemotherapy was supplemented by other measures. In 6 other cases, after an initial regression of the clinical symptoms and clearing on roentgenologic examination lasting two to three months, an exacerbation or a new spread occurred. The conclusion is drawn that TB 1 may interrupt the progression of the disease but it is unable to arrest it.—*Ergebnisse langdauernder TB I-Medikation bei progredienter Lungentuberkulose, K. H. Herold, Deutsche med. Wchnschr., July 14, 1950, No. 27/28: 948.*—(*L. Molnar*)

Clinical Appraisal of Neomycin.—Neomycin therapy was investigated in 63 patients. The drug did not exert a demonstrable effect in the 7 cases of tuberculosis that were treated. Infections due to *Proteus* and to other gram-negative bacilli were favorably affected by this antibiotic. In no instance did neomycin-resistant variants appear during the course of treatment. Demonstrable levels of neomycin were present in the serum, pleural fluid, and spinal fluid of many of the patients studied. In the doses used, neomycin undoubtedly caused kidney and eighth nerve damage to several patients. In view of the ototoxic and nephrotoxic effects of neomycin, this drug cannot be recommended for general use (Authors' summary).—*A clinical appraisal of neomycin, B. A. Waisbren & W. W. Spink, Ann. Int. Med., November, 1950, 33: 1099.*—(*T. H. Noehren*)

Treatment of Pneumococcic Pneumonia.—Although the efficiency of penicillin in the pneumonias caused by pneumococci is a well-established fact, there is no unanimity of opinion regarding the optimal dose which should be employed. In this study, 686 patients with typed pneumococcic pneumonia were treated with penicillin; 36 (5.2 per cent) died. The case fatality rate among 283 patients treated with 600,000 units of penicillin in oil and beeswax or 600,000 units of procaine penicillin in oil twice a day was 5 per cent, as compared with a case fatality rate of 5.4 per cent among 403 patients to whom penicillin was administered intramuscularly or orally in doses which produced lower average blood concentrations. The fatality rates in bacteremic patients, in patients with complicating diseases, and among patients in the different age groups were comparable for the two series. It is concluded that the administration of 600,000 units of repository penicillin twice a day in pneumococcic pneumonia yields results practically identical with those obtained with the more commonly employed lower dosage

forms.—*The treatment of pneumococcic pneumonia with large doses of repository penicillin compared with lower doses of penicillin: A study of 986 patients, H. F. Dowling, M. H. Lepper, & H. L. Hirsh, Am. J. M. Sc., July, 1950, 220: 17.—(W. J. Steininger)*

Aureomycin for Common Cold.—In a study conducted at a military hospital, groups of patients with colds were treated with aureomycin and placebos, respectively. No significant difference in the proportion of cures was observed.—*Aureomycin in the treatment of the common cold, R. J. Hoagland, E. N. Deitz, D. W. Myers, & H. C. Cosand, New England J. Med., November 16, 1950, 243: 673.—(A. G. Cohen)*

LABORATORY STUDIES

Virulence of Tubercle Bacilli.—*In vitro* observations have suggested that an oil-soluble cellular surface constituent of tubercle bacilli, called the "cord factor," is partly responsible for properties associated with the virulence of the organisms. Because young cultures of tubercle bacilli yield more cord factor than older ones of the same strain, it was predicted that these young cultures would be more virulent for susceptible animals. To test this, tubercle bacilli of the human strains H37Rv and Jamaica No. 22 and of a bovine strain Vallee were cultured in Tween-albumin liquid medium. Inoculation suspensions were standardized to a given optical density. Groups of mice were then infected with equal numbers of living bacilli from three-day-old or three-week-old cultures. Injection of the older organisms resulted in the classical picture of mouse tuberculosis; the mice survived for 100 days or longer and had no myocardial lesions. The mice which received the young bacilli died within thirty days from an acute, septicemic type of disease, with lesions in almost every organ. Tuberculous myocarditis seemed to be the most serious effect and was the immediate cause of death. The lesions contained masses of tubercle bacilli and histologically were characteristic of fresh inflammatory foci without any productive or necrotic tissue reaction. To prolong the survival time of mice infected with young bacilli to that of animals receiving the three-week-old culture, the infecting dose had to be diluted ten or fifteen times. To achieve an early death for the animals infected with the older cultures, the animals had to be infected with ten times the standard dose of the bacteria. The results with the three-day-old cultures were the same irrespective of the strain of mice or the strain of bacteria. A similar rapidly progressive infection was observed in rabbits infected with bacteria from young cultures regardless of the type of bacilli used. The symptoms corresponded to those of the "Yersin" type of tuberculosis. In very young cultures slim, poorly acid-fast tubercle bacilli predominate. Although these experiments indicate that virulence may be related to the content of cord factor, they do not explain the existence of *Mycobacteria* which produce cord factor and yet are not virulent, such as the alternated strains of the BCG type. These strains do not cause progressive tuberculosis in a normal man or animal, but can multiply in a host organism and can cause fatal tuberculosis in a silicotic guinea pig.—*Studies on the virulence of tubercle bacilli: The relationship of the physiological state of the organism, to their pathogenicity, H. Bloch, J. Exper. Med. December 1, 1950, 92: 507.—(J. S. Woolley)*

Hemagglutinin Test.—Although the serum of healthy rabbits and guinea pigs gave no agglutination reaction with sensitized erythrocytes, intravenous inoculation with living or dead, virulent or nonvirulent tubercle bacilli always produced a specific hemagglutinin reaction. The titer of hemagglutination was higher when living organisms were inoculated. Streptomycin had a definite effect on this titer; animals inoculated with 0.1 mg. of the Ravenel strain and treated daily with streptomycin, 25 mg., showed a drop of the titer from 1:2,048 to 1:64. An intracutaneous tuberculin test did not modify the agglutination titer; intramuscular or intravenous injection of 20 mg. of tuberculin gave an elevation of the titer. In a veterinary survey, 80 per cent of the cattle with significant tuberculous lesions ex-

hibited positive hemagglutinin tests; the reaction was inconstant in caseocalcific adenopathies. Serum from healthy humans clinically and roentgenologically free from tuberculosis sometimes showed positive hemagglutinin reactions, the titer usually being less than 1:16. This titer was therefore arbitrarily chosen as the dividing line between positive and negative reactions. By this criterion, 96 per cent of healthy persons had negative reactions; the cause could not be determined for the 4 per cent false positive reactions which were unrelated to tuberculin allergy. Of 46 patients with nontuberculous pulmonary disease, 4 had positive hemagglutinin tests. Of 450 patients with caseocavernous tuberculosis, 77 per cent had positive hemagglutinin reactions and 23 per cent had a titer below 1:16. It was observed that the percentage of positive reactions was higher with some antigens. The reaction was not found to be a useful test to determine the activity of tuberculous lesions. Two to four weeks after BCG vaccination, 27 of 45 persons showed a positive hemagglutinin test which persisted only for two to three months. —*Intérêt de la réaction d'hémagglutination pour le diagnostic de la tuberculose et le controle de la vaccination par le BCG, C. Gernez-Rieux & A. Taquet, Rev. de la tuberc., 1950, 14: 676.*—(*V. Leites*)

PUBLIC HEALTH AND EPIDEMIOLOGY

Tuberculosis Survey.—The city of Boston has a slightly higher tuberculosis rate than the nation as a whole. The rate is greater than that of more large American cities and of almost all the Eastern cities. The total population is about 750,000, and contains about 3 per cent of nonwhite persons. A total of 556,042 persons were X-rayed on 70 mm. film. Intrathoracic abnormalities were disclosed in 2.73 per cent, including tuberculosis in 0.76, suspected tuberculosis in 0.77, nontuberculous chest diseases in 0.58, and cardiac conditions in 0.57 per cent. Retakes on 14 by 17 films and clinical examinations were made for 9,372 persons. Definite abnormalities were revealed in 7,254, including tuberculosis in 4,122 (active in 247), suspected tuberculosis in 443, nontuberculous chest diseases in 2,406, and cardiac disorders in 275. There were 402 cases in which cancer was suspected. Of these, the diagnosis has thus far been proved in 52, while many others are still under investigation.—*The results of the Boston chest x-ray survey, J. H. Cauley, New England J. Med., October 20, 1950, 243: 631.*—(*A. G. Cohen*)

Tuberculin Testing in the Navy.—Since January 1942 fluorograms of the chest have been a part of the routine examination to determine physical fitness of inductees and applicants for the Navy and Marine Corps. In the spring of 1948 the tuberculin test was made a part of this routine. This report deals with the results of tuberculin testing of recruits at one Marine Corps and 2 naval training centers during the last nine months of 1948. The intracutaneous method of testing was used. Of the 79,393 midshipmen and Navy and Marine Corps recruits tested, 9.7 per cent had a positive reaction to a dose of 0.0001 mg. PPD. The incidence of positive reactors in Navy recruits was slightly higher (10.4 per cent) in men who enlisted in the southern and western states as compared to the incidence (9.0 per cent) for men who enlisted in the north central and northeastern states. The second strength of PPD (0.005 mg. per dose) produced a high incidence of presumably nonspecific reactions in a group of 500 Navy recruits tested. It is recommended that caution be used in applying these results to the same restricted age groups of the general population because of certain factors which influence the selection of midshipmen and recruits for the service.—*Tuberculin testing of midshipmen and recruits of the Navy and Marine Corps, R. O. Canada & R. W. Babione, U. S. Armed Forces M. J., September, 1950, 1: 971.*—(*T. H. Noehren*)

Tuberculosis in Medical Students.—The results of a tuberculosis case-finding program in the Student Health Service at the University of Wisconsin from 1934 to 1947, inclusive, are presented. Among the graduates of the medical school from 1934 to 1943, 19 of 188 students (10.1 per cent) who were originally

tuberculin-negative developed tuberculosis. The incidence of clinical tuberculous infection among those who converted from a negative to a positive skin test was 13.7 per cent. In the same class there were only 2 (2.1 per cent) of the original 95 tuberculin reactors who developed tuberculosis. Among the medical school graduates from 1944 to 1947 inclusive, 6 of the 44 originally tuberculin-negative individuals (13.6 per cent) have developed tuberculosis. The incidence of tuberculous lesions among the converters was 17.6 per cent. Among 46 original tuberculin reactors, 2 (4.3 per cent) have tuberculosis. Among the student nurses, 8 of the 59 converters (13.6 per cent) have had tuberculous lesions, while of the 33 original tuberculin-positive group, only one student (3 per cent) has developed a tuberculous lesion. Since 1942, 245 medical students and 174 student nurses have been vaccinated with BCG. There have been no systemic reactions, local abscesses, or regional adenitis. With 2 exceptions, all of the vaccinated individuals have become tuberculin sensitive. The tuberculin reactions have remained positive throughout the period of professional training. Only 2 vaccinated students have developed pulmonary lesions which might be considered tuberculosis.—*Tuberculosis in student nurses and medical students at the University of Wisconsin, H. A. Dickie, Ann. Int. Med., October, 1950, 33: 941.*—(*T. H. Nochren*)

BCG Vaccination in Family Groups.—This study of the efficiency of BCG vaccine embraced 348 families with 940 children. Of these, 479 were inoculated with BCG and 461 kept as controls. The nonvaccinated series represented, as a whole, a higher age group than the vaccinated series. Thus, 47.4 per cent of the vaccinated children and only 1.7 per cent of the controls were six months of age or younger; and 21.9 per cent of the nonvaccinated and only 2.7 per cent of the vaccinated, 10 years of age or older. Tuberculosis morbidity was 3.13 per cent among the vaccinated and 13.4 per cent among the nonvaccinated. Tuberculosis mortality was also 4.2 times as large among the controls as among the vaccinated. The fact that vaccinated children were examined several times while 45 per cent of the nonvaccinated were seen only once supports the belief that cases of disease may possibly have been overlooked among the latter rather than among the former. To make the series more comparable, all cases of disease occurring in children over fifteen were ignored. Chances of exposure to a known tuberculosis environment were somewhat greater for the controls: 62.04 to 49.68 per cent.—*Resultados da vacinação tuberculosa em 384 famílias, A. MacDowell filho, Rev. brasil tuberc., March-April, 1950, 18: 157.*—(*A. A. Moll*)

Dried BCG.—Results obtained with freeze-dried BCG confirm Leshchinskaya's, Rosenthal's, and Ungar's reports to the effect that lyophilization has definite advantages over older methods, especially from the standpoints of the maintenance of stocks, distribution and uniformity of cultures. As suspending fluids for BCG intended for drying, preference was given to skimmed milk because of its availability. Glucose and lactose solutions as recommended by Leshchinskaya and Rosenthal proved less satisfactory. In comparing the number of organisms before and after drying, a 44 per cent loss was found. Weight, however, did not decrease, thus showing complete survival of the cultures submitted to the process. The main handicap of lyophilization is the formation of crystals which may kill the bacilli. This may be minimized by rapidly cooling the material.—*BCG seco, D. M. Cardoso & W. F. Almeida, Rev. brasil. tuberc., March-April, 1950, 18: 119.*—(*A. A. Moll*)

Oral BCG in Allergic Individuals.—The oral use of BCG was studied at S. Paulo, using three main groups of subjects. The first consisted of 256 inmates of a home for the blind, all apparently free from tuberculosis; 120 were positive and the rest negative to tuberculin. The entire negative population and 99 of the 120 positive reactors were vaccinated with BCG. The other 21 served as controls. The oral dosage of BCG vaccine varied from 0.3

to 3.0 gm., given in most instances in a single dose but in 47 cases spread over a number of weeks. The second group included 322 contacts from 107 families of patients enrolled at a tuberculosis dispensary. If these, 42 were anallergic and 280 allergic to tuberculin. A total of 187, 32 in the first category and 155 in the second category, were given BCG after exhaustive preliminary examinations to exclude the presence of tuberculosis. BCG was given orally in monthly 0.2 gm. doses, the total dosage varying from 0.2 to 4.2 gm. averaging 1.2 gm. Finally, 50 tuberculin-positive children, 42 of them in a known tuberculous environment, were vaccinated with BCG. The dose was 0.2 gm. orally at fourteen-day intervals, the total dosage varying from 0.8 to 2.6 gm. The first group was kept under observation for three years, the second from six to thirty-six months, and the third from three to eight months. All those vaccinated were subjected to periodic clinical, roentgenologic, and laboratory examinations. At no time during or after the administration of the vaccine were signs or symptoms detected suggesting any noxious action by BCG. Nontuberculous diseases showed about the same incidence in both the vaccinated allergic individuals and in the allergic controls. In the second group, among families under observation from twenty-four to thirty-six months, 7 cases of tuberculosis developed, 6 being among controls. The seventh case was in a vaccinated tuberculin-positive individual and occurred seven months after completing the vaccination, without differing in any respect from the 6 cases among the controls. Attenuation of allergy was found during the vaccination process, amounting in some cases to complete negativation of tuberculin sensibility. The safety of BCG vaccination in allergic persons and the prevailing conditions in many parts of South America suggest the advisability of using BCG without preliminary tuberculin testing. A trial of this sort has already been made in two communities in the interior of the state of S. Paulo. A recent re-examination of these two groups verified again the safety of the method.—*Resultados ulteriores da vacinação BCG por via digestiva em individuos tuberculino positivos, J. Rosemberg, Clín. Tisiol., January–March, 1950, 4: 1.*—(*A. A. Moll*)

Skin Sensitivity to Fungus Antigens.—University students and other groups were tested intradermally with tuberculin, histoplasmin, and coccidioidin in an attempt, among the first in Europe, to study the sensitivity to fungus antigens in Spain. Of 1,842 first-year students, there were 126 (6.82 per cent) negative reactors to 1 mg. of OT. This incidence of negative-reactors was six times larger than that in 1939 indicating a certain improvement in the situation since the Spanish Civil War. Pulmonary and hilar calcifications were noted in over 50 per cent of the cases. Among 47 nonreactors, there were 11 individuals with roentgenologic signs of calcification. The failure of individuals with calcifications to react to adequate doses of tuberculin is interpreted as a conversion of a once positive test to negative after the extinction of the primary lesions. Reports about the frequency of sensitivity to histoplasmin and to coccidioidin in certain regions of the United States are open to criticism because the method of tuberculin testing was not standardised and because there are still many uncertainties in the technique and interpretation of skin testing with fungus antigens, especially histoplasmin. The large number of cases with pulmonary calcifications which do not react to tuberculin may be readily explained by the epidemiologic conditions prevailing in the United States; these favor the extinction of the first infection because the sources of superinfection are diminished. Among 930 individuals tested with histoplasmin, not a single positive reaction was observed. Of 484 individuals tested with coccidioidin, there were 3 with an infiltration about 3 mm. in diameter at the site of the injection considered as doubtfully positive. In view of the geographical similarities of certain areas in Spain with those American regions where coccidioidomycosis is endemic, further studies with coccidioidin testing are recommended.—*Tuberculina, histoplasmina, coccidioidina, J.*

Zapatero, Rev. españ. de tuberc., June, 1950, No. 183: 363.—(L. Molnar)

Histoplasmosis in Brazil.—Our present knowledge of the prevalence of histoplasmosis infection is, to a large extent, a by-product of mass chest surveys for tuberculosis. Of 1,342 persons, including 1,062 children one to seventeen years old, examined in a tuberculosis dispensary in the city of Rio de Janeiro, 925 (67.4 per cent) reacted positively to tuberculin and 145 (10.6 per cent) to histoplasmin. Only 52 of these 145 were definitely known to have been born and reared locally; the remainder were from widely separated parts of Brazil but mostly from the central and northeastern areas. In the case of histoplasmin, positive rates varied from 2.7 per cent among 377 preschool children and 2.9 per cent among 403 children six to twelve years old to 28.3 per cent among 46 middle-aged adults and 27.1 per cent among 214 younger adults. Among the 145 histoplasmin-positive cases, 136 (93.1 per cent) were also tuberculin-positive. In all, 80 individuals positive both to histoplasmin and tuberculin as well as 8 histoplasmin-positive, tuberculin-negative individuals had normal pulmonary roentgenograms. Only 11 persons positive both to histoplasmin and tuberculin had definite roentgenographic signs of pulmonary disease. The remaining 46 of the histoplasmin-positive group showed roentgen signs of pulmonary calcification similar to those areas of the United States where histoplasmosis is endemic. Only 2 patients negative to tuberculin and positive to histoplasmin revealed pulmonary calcification. No individual negative to both substances showed residual pulmonary calcification. In a small group chosen for detailed study, cases of both histoplasmin positivity and negativity were found among children in the same family.—*Sôbre a histoplasmose: I. Conceito moderno: Histoplasmose maligna e benigna. Histoplasmose infecção. Histoplasmose pulmonar benigna e residual. II. Estudo baseado em 1,372 indivíduos com 145 reatores positivos à histoplasmina na cidade do Rio de Janeiro, A. de Carvalho, Clín. Tisiol., January–March, 1950, 4: 45.—(A. A. Moll)*

Ultraviolet Disinfection of Air.—Ultraviolet irradiation of school rooms effected a median reduction in the air's bacterial population of 42 per cent. The number of bacteria in the room increased with the activity of the occupants of the semi-enclosed space. There was an explosive epidemic of measles in the unirradiated schools. The incidence of the infection was the same in the irradiated classrooms but the epidemic was protracted and there was internal evidence suggesting that the school bus was a secondary source of infection. Since the epidemic was caused by a virus, no direct application of the bacterial population studies can be made to the epidemiologic findings.—*Bacteriologic studies in disinfection of air in large rural central schools, Ultraviolet irradiation, F. W. Gilcreas & H. V. Roberts, Am. J. Pub. Health, July, 1950, 40: 808.—(M. B. Lurie)*

JACKSON BRONCHOSCOPES

by Pilling

Pilling supplies the complete line of genuine Jackson bronchoscopes . . . *the approved models*, standard for use with all equipment in the standard Jackson-type Clinic.

Pilling makes *every size* and *every type* of bronchoscope devised by Dr. Chevalier Jackson, and makes them—for years of service—from Broncalloy.

Broncalloy instruments are lighter, yet stronger—thin but rigid—smooth in surface, bite-proof and resistant to corrosion, distortion and damage.

Standard Jackson Bronchoscopes, as illustrated, all sizes from 4 mm. x 20 cm. to 9 mm. x 40 cm., with 2 light carriers and 2 lamps. Light carriers are interchangeable in bronchoscopes of equal length.

Special sizes can be made to order. Consult us.

Order direct from

George P. Pilling and Son Company

3451 WALNUT STREET • PHILADELPHIA

Headquarters for

INSTRUMENTS FOR BRONCHOESOPHAGOLOGY

A Standing Invitation: When in Philadelphia, visit our new salesroom. Free parking for doctors on our private lot.

Now on the Press

TWELVE-YEAR CUMULATIVE INDEX AMERICAN REVIEW OF TUBERCULOSIS

Every Review subscriber will welcome the news that a new Cumulative Index is now being printed which will afford ready access to the wealth of scientific and clinical data embodied in the 144 issues published between January 1937 and December 1948. The new index provides almost 10,000 cross-references to more than 1,800 papers by some 3,000 authors.

Each of the 1,800 papers is fully indexed by author, title, subject, date of issue and page number. More than 500 subject headings arranged alphabetically assure quick, easy location of any required article.

The Cumulative Index is a paper-covered volume of 200 pages in the same size as the Review itself, adaptable for binding in series with bound volumes of the Review. A price has been established which represents merely production and handling expenses—$2.50 postpaid (25 cents extra for foreign postage).

IMPORTANT NOTE: A few copies of the 1917–1936 Cumulative Index, covering the contents of the American Review of Tuberculosis during its first 20 years of publication, are still available at a reduced price of $1.00. To receive your copy, note your request on the order form.

AMERICAN REVIEW OF TUBERCULOSIS
1790 Broadway, New York 19, N. Y.

Send me _____ copies of the new Cumulative Index for the 12-year period 1937–1948 inclusive. I enclose payment at the rate of $2.50 a copy (25 cents per copy additional foreign postage).

NAME _____

CITY and STATE _____

Use this convenient order form to send your order — TODAY.

EMERSON
LUNG IMMOBILIZER

In the "equalizing pressure chamber" developed by Alvan L. Barach, M.D., the patient is enabled to cease completely all breathing motion, while a rhythmic alternation of air pressure and partial vacuum (+ and — 60 mm. Hg) produces effective pulmonary ventilation. This total lung rest has been found to promote closure of cavities in cases unresponsive to other forms of accepted therapy.

Addressing the College of Chest Physicians in June, 1950, Dr. A. L. Barach of New York and Dr. G. L. Bellis of Winnebago, Wisconsin, presented reports on the treatment of 67 patients, mainly advanced, bilateral cases. Favorable results were obtained in 49 of the 67. Some patients had remained apparently cured for as much as nine years.

For further information, write:

J. H. EMERSON CO.
22 Cottage Park Ave., Cambridge 40, Mass.

Maryknoll
SANATORIUM
(Maryknoll Sisters)

MONROVIA, CALIFORNIA

• A Sanatorium for the treatment of tuberculosis and other diseases of the lungs. Located in the foothills of the Sierra Madre Mountains, Southern exposure. Accommodations are private, modern, and comfortable. Rates are moderate. General care of patient is conducive to physical and mental well being.

SISTER MARY PIETA
Superintendent

E. W. HAYES, M.D.
Medical Director

Present Concepts of Rehabilitation in Tuberculosis

by NORMAN C. KIEFER, M.D.

420 pages, cloth cover $3.50

In this volume there is brought together, for the first time, an accurate summary of world research and achievement in every area of rehabilitation during the last decade.

More than 1,000 original papers are abstracted in this book, and in every case the salient features of each have been brought together in classified sections to provide a complete picture of approaches, procedures, and results

A bibliography of more than 1,000 items supplies reference to basic sources, and a particularly comprehensive index facilitates the location of specific information.

Your order can be filled promptly.

NATIONAL TUBERCULOSIS ASSOCIATION
1790 Broadway, New York 19, N. Y.

IN THE AIM TOWARD

Prevention of Tuberculosis Recurrence

Wide clinical observations support the assumption long held that malnutrition predisposes to tuberculosis and that good nutrition tends to prevent tuberculosis activity in patients in whom the disease is quiescent.[1]

The dietary supplement, Ovaltine in milk, provides a reliable means for assuring optimal adequacy of the diet of the tuberculous patient. It can readily supplement even grossly deficient diets to full adequacy. When distinct food likes and dislikes handicap the nutrition of the patient, the delicious flavor of Ovaltine beverage not only invites its ready acceptance but helps make the diet interesting. It richly furnishes biologically complete protein, minerals—especially calcium and iron—and all the essential vitamins. It is easily digestible, and its food energy is quickly available.

For permitting choice of flavors according to preference, Ovaltine is provided in two forms—plain and chocolate flavored. Both are virtually equivalent in supplemental amounts of vitamins and minerals.

Note the wealth of nutrients furnished by Ovaltine in milk as shown in the table.

1. Wohl, M. G.: Dietotherapy, Chapter 26 in Clinical Nutrition, edited by Jolliffe, N.; Tisdall, F. F. and Cannon, P. R., for the Food and Nutrition Board, National Research Council, New York, Paul B. Hoeber, Inc., 1950.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk, provide:*

PROTEIN	32 Gm.	VITAMIN A	3000 I.U.
FAT	32 Gm.	VITAMIN B_1	1.16 mg.
CARBOHYDRATE	65 Gm.	RIBOFLAVIN	2.0 mg.
CALCIUM	1.12 Gm.	NIACIN	6.8 mg.
PHOSPHORUS	0.94 Gm.	VITAMIN C	30.0 mg.
IRON	12 mg.	VITAMIN D	417 I.U.
COPPER	0.5 mg.	CALORIES	676

*Based on average reported values for milk.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.

The Workmen's Circle Sanatorium

Liberty, New York

The Workmen's Circle Sanatorium, Liberty, N. Y., a modern, thoroughly equipped institution situated in the heart of the Catskills for treatment of tuberculosis and other diseases of the lungs.

Rates are $45 per week inclusive of all charges.

For further information write to:

SAMUEL LIPSTEIN, M.D.
SUPERINTENDENT AND MEDICAL DIRECTOR

ALUM ROCK SANATORIUM

SAN JOSE, CALIFORNIA

Telephone Clayburn 8-4921

A non-profit sanatorium for the treatment of Tuberculosis and other diseases of the chest.

Medical Director
Roland H. Worden, M.D.
Associate Medical Director
C. Gould Scarborough, M.D.

Visiting Medical Staff:

Harold Gayon Tribble, M.D., Oakland
Cabot Brown, M.D., San Francisco
J. Lloyd Eaton, M.D., Oakland
H. Corwin Hinshaw, M.D., San Francisco
Gerald L. Crenshaw, M.D., Oakland
Glenny N. Flynn, M.D., San Francisco
Ian Gourley, M.D., Oakland
James Robert Wood, M.D., Oakland
W. Dale Patterson, M.D., Oakland

Consulting Pathologist
R. Gwyn Roberts, M.D., San Francisco

NATIONAL TUBERCULOSIS ASSOCIATION

Annual Meeting — May 15–18, 1951

Cincinnati, Ohio

The annual meeting of the National Tuberculosis Association will be held in Cincinnati, Ohio, May 15–18, 1951. The Netherland Plaza Hotel will be headquarters.

Some 1500 rooms have been promised by the hotels listed below for the accommodation of those attending the meeting. Arrange to share a double room if possible.

Application for room reservations should be made directly with the hotel of your choice.

Hotel	*Address*	*Single*	*Double*
NETHERLAND PLAZA	Carew Tower	$4.00–$10.00	$9.00–$13.00
SHERATON-GIBSON	421 Walnut Street	$4.00–$12.00	$7.50–$12.00
TERRACE PLAZA	15 West Sixth Street	$7.00–$12.00	$10.00–$15.00
SINTON HOTEL	4th at Vine Street	$4.00–$10.00	$8.00–$12.00
FOUNTAIN SQUARE	420 Vine Street	$4.00–$5.50	$8.00–$8.50
PALACE HOTEL	6th at Vine Street	$2.50–$4.00	$5.00–$7.00
METROPOLE HOTEL	609 Walnut Street	$3.00–$6.00	$6.50–$10.00
BROADWAY HOTEL	4th and Broadway	$3.50	$5.50–$6.50
ALMS HOTEL	Victory Pkwy. & McMillan	————	$7.50–$15.00

See March issue of NTA BULLETIN *for preliminary program.*

THE PANRAY CORP.

Announces

Gensalate Sodium

A New and Better Drug for the Treatment of Rheumatic Diseases

GENSALATE SODIUM is a highly purified form of the sodium salt of 2,5-dihydroxybensoic acid (sodium gentisate). It acts promptly and effectively to reduce fever, pain, swelling, sedimentation rate, white blood count and other symptoms associated with the rheumatic diseases. In this, its action is similiar to that of salicylates.

GENSALATE SODIUM, however, is superior to salicylates, in that clinical evidence has shown it to be *far less toxic*. In daily doses of 10 grams administered over long periods of time, no deafness, tinnitus, tachypnea, lung edema, severe gastric disturbances or adverse blood changes have been noted. On the other hand, salicylates administered in similiar dosage have often given rise to these toxic manifestations.

GENSALATE SODIUM is especially indicated in acute rheumatic fever, rheumatoid arthritis, ankylosing spondylitis, fibromyositis and osteoarthritis.

DOSAGE: *In rheumatic fever*, orally, 2 gms. every 3 hours for at least 10 days after temperature becomes normal. In conditions requiring prolonged therapy, not over 10 gms. daily.

Ref. 1. Meyer and Regna: Science — 102, (Sept. 16th, 1945).
2. Schneider, Haddad & Megibow: Circulation, 2:3. (August 1950).
3. Gorsuch: Medical Women's Journal, 57:9, (Sept. 1950).
4. Meyer and Regna: Modern Concepts of Cerebrovascular Disease XVII:No. 2 (Feb. 1949).
5. Cornell, Seeger & Tsuy: Proc. Soc. Exp. Biol. & Med. 59: 200, (June 12th, 1950).
6. Orr: Rheumatism 9: 1, (March, 1950).
7. Orr: Rheumatism 9: 29, 1401 (June 28, 1949).

Producers of PARASAL® and PARASAL® SODIUM for the treatment of tuberculosis

GENSALATE SODIUM is supplied as 0.5 gm. tablets in bottles of various sizes, and is available on prescription. For samples and literature, pin this coupon to your prescription blank or letterhead and mail at once.

THE PANRAY CORP.
349 Canal St., New York 13, N. Y.

Gentlemen: Please send me literature and samples of GENSALATE SODIUM, the new anti-rheumatic drug.

G